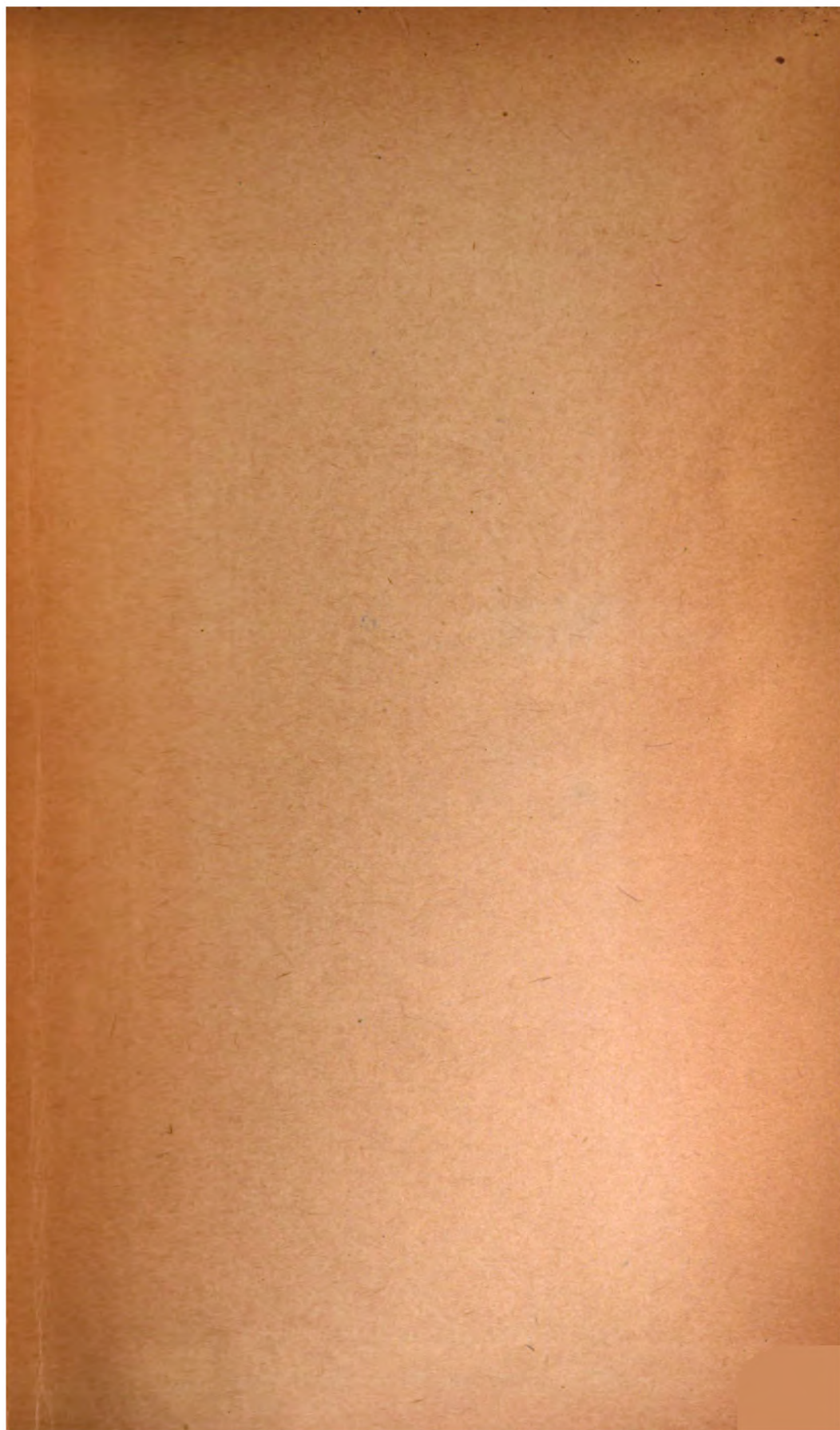


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# FATTY STOOLS FROM OBSTRUCTION OF THE LACTEALS.

## WITH A NOTE ON THE CÆLIAC AFFECTION \*

By J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

THE occurrence of fatty or chylous forms of diarrhoea has been recognised for many centuries. The works of Aretaeus<sup>1</sup> contain a reference to "The Cœliac Affection" in which the characteristic stool is thus described:—

" . . . Its colour is white and without bile; it has an offensive smell, and is flatulent; it is liquid, and wants consistence from not being completely elaborated, and from no part of the digestive process having been properly done except the commencement."

There do not, however, appear to have been any detailed observations on the nature and pathogenesis of the symptom until the early part of the last century. Oser<sup>2</sup> mentions Kuntzmann as having been the first to associate fatty stools with pancreatic disease in 1820. In 1832 Bright,<sup>3</sup> who apparently was not aware of Kuntzmann's description, brought forward further evidence of the association between pancreatic and duodenal disease, and the presence of fat in the stools. Twenty-three years later Gull,<sup>4</sup> writing in the *Guy's Hospital Reports*, described fatty diarrhoea in association with disease of the mesenteric lymphatics, and we may justly claim that the differentiation of the two main varieties of fatty diarrhoea is largely due to the careful observations of the two last-named physicians.

Gull's summary of the matter merits full quotation:—

" With their imperfect means of observation," he says, " the older physicians often surpassed us in their knowledge of symptoms; and though their pathology, from want of chemistry and the microscope, had a vague expression about it, it was more or less true to nature. Diarrhoea chylosa and fluxus cœliacus were recognised by them, and attributed to some impediment in the absorbent system, whereby the chyle was left to escape with the fæces, an opinion which appears to be well founded,

\* Based on a communication given at the Meeting of the Association of Physicians of Great Britain and Ireland. Edinburgh, May 1923.

though it is probable they often mistook inflammatory exudation for chyle. Modern authors have passed over the subject, or have treated it lightly.

“The normal absorption of fatty matters is prevented from two causes; either from a defect in the digestive or emulsifying process, or from disease of the absorbent system. The instances of fatty stools from disease of the pancreas and the duodenum, as described by Dr. Bright and others, belong to the former, and are characterised by the fat passing from the intestines, more or less separate from the general mass of the fæces, and concreting upon them; but in the latter case, where the disease is in the absorbent system, the fat, *being emulsified, becomes incorporated with the evacuation, and is consequently not so easily recognised*. If, however, there be, with defective absorption, an inflammatory condition of the mucous membrane and diarrhœa, the oily matters rise to the surface of the evacuation as a creamy film, and produce the pale, chalky, and soapy appearance so characteristic of chronic muco-enteritis and mesenteric disease.”

In describing a case of fatty diarrhœa due to tuberculosis of the mesenteric glands he says :—

“The bowels were generally moved three times in the twenty-four hours. The evacuations were pultaceous or liquid, of a dull chalky colour, frothing like soap when a stream of water was poured on them. Under the microscope they were seen to contain muscular fibre in different stages of disintegration, starch cells, etc., and finely divided oily and granular matter like chyle, and inflammatory exudation.”

We can add little if anything to Gull's conclusions as to the main causes preventing “the normal absorption of fatty matters.” The interest which has been stimulated in recent years in the various special tests for pancreatic efficiency would seem, on the experience of the cases described hereunder, to have blinded us somewhat to the value of the simpler methods of observation and deduction employed by “the older physicians.”

During the past three years I have had the opportunity of studying two cases of fatty diarrhœa in adults, and one in a child. In both of the adult cases, in spite of careful clinical and laboratory investigations, the true cause of the condition escaped recognition prior to the performance of a laparotomy, and a diagnosis of pancreatic disease had been entertained.

It should, I believe, have been possible in each instance to predict the correct diagnosis on clinical grounds. I have therefore thought it worth while to place on record an account of the cases in question. In doing so I am further actuated by the



fact that Case 1 showed features so characteristic of what has been described as the cœliac disease in children that I hoped that it might serve to throw some light upon the causal pathology of that obscure malady.

*Case 1.*—A young woman, aged twenty-three. Admitted for chronic diarrhœa and tetany. Since she was a baby patient has been subject to attacks of diarrhœa. In recent years these have become more continuous, and latterly there has been little or no intermission. Often she passes six or more fluid stools a day. The diarrhœa is associated with pain above the umbilicus. In spite of this prolonged ill-health she has a good appetite and has not lost weight. When over-tired, and invariably during the menstrual periods, she has attacks of true tetany with carpopedal spasms. These have been becoming worse and more frequent; last from two to six hours; and are relieved by morphia. Her doctor (Dr. H. L. Burton) thinks they have been fewer while she has been taking parathyroid tablets. Patient looks younger than her years; is of small stature; and has a "pink and white" complexion, with small dilated venules on the cheeks. The whole abdomen, but especially the lower part, is rather full and tense. The abdominal reflex is brisker on the right. *The stools are enormously bulky, frequently filling almost half an ordinary bed-chamber as the result of a single evacuation. They are rancid, greyish, and porridgy in consistency. They show excess of fatty matters and meat fibres. Under the microscope crystals and soapy fragments were observed. Quantitative estimations of the fat in the stools were not performed.*

Subjective symptoms improved as the result of rest. Pancreatin was given without effect.

A few weeks after she came under observation patient developed tenderness in the right iliac fossa, and it was decided to explore the abdomen. The operation was performed by Mr. L. Bromley, who reported as follows: "The appendix was adherent to the lower end of the mesentery. It was removed and found to show a few scattered submucous hæmorrhages, and contained a bead of pus at its tip. The mesentery of the small intestine contained innumerable caseating tuberculous glands. *The lymphatics were looped and tortuous, white in colour, being distended with fat droplets, the passage of which was obstructed by the condition of the mesenteric glands.*" The distended lacteals indeed presented a remarkable appearance, their calibre in places almost equalling that of a tooth-pick. Their condition at once explained the nature of the long-standing fatty diarrhœa.

The patient was treated for about a year with rest, open-air, and a diet as nearly as possible fat-free. For a time there was abdominal discomfort and pain, and a small fluctuating area near the umbilicus, presumed to be due to breaking down glands, developed. Radiographic evidence of peribronchial glandular tuberculosis was also forthcoming, and for a time some patches of lichen scrofulosorum were present on the skin. On

the fat-free diet the stools became formed and darker in colour, and were reduced to one or two per diem, but they still remained abnormally bulky.

Finally the patient's general condition improved greatly, and she has now been actively employed with light duties for many months. There is no actual diarrhœa. Minor tetanic spasms have recurred from time to time. Calcium is now being given in attempt to control this symptom.\* Throughout the whole period of observation the temperature only very rarely rose above normal.

It is difficult to avoid the conclusion that this patient had a condition of *tabes mesenterica* dating from early childhood. For six years, at any rate, she had been subject to tetany, and the diarrhœa started many years before this. Nevertheless, appetite and general nutrition had been good on the whole, and she had been working hard before coming under observation.

The tetany was presumed to be associated with periods of acute calcium deficiency resulting from the excessive excretion of calcium soaps; it was consequently worse when the diarrhœa was worse, and disappeared when the diarrhœa was relieved by giving a fat-free diet.

The features which might have helped to establish the diagnosis were: (1) The naked eye appearance of the stools which were of the bulky, greasy, pultaceous type described by Gull, and contained no separate oil or coagulum; (2) the presence of crystals and soaps, suggesting that absorption rather than digestion was chiefly at fault; and (3) the tetany, which presumably should not occur with the passage of unsplit fats as in true pancreatic deficiency.

The presence of meat fibres merely expressed the diarrhœic state.

*Case 2.*—A man aged thirty-six. Admitted for great loss of weight, hunger, thirst, abdominal fulness, and the passage of copious light-coloured stools. Previous history: Feeble at birth, and before the age of seventeen had pneumonia, tuberculous glands in the neck, tuberculous disease of the left ankle-joint, and an operation on the left mastoid antrum. After the age of eighteen he became very fit. He was always a very large eater, though his food did not seem to fatten him. One sister has pulmonary tuberculosis. He joined the Army during the War and served in France, Egypt, and Salonika. Appendicectomy at Salonika in 1915. In 1920 he went to Canada. At this time he was feeling rather weak and had "acidity" and

\* 5-12-23. Within forty-eight hours of starting calcium lactate, gr. x, three times daily, minor facial and carpal spasms, present for some time, have ceased. Chvostek's sign, however, is well marked.

lower abdominal discomfort about one hour after meals. Next summer he went away for a holiday, and lived on farm-produce, but the acidity and fulness increased rather than diminished. In September 1921 he had violent diarrhoea and passed ten motions a day "of the colour of modeller's clay." He was investigated in Toronto, and a diagnosis of "hyperacidity" was made. Another physician said he had phthisis and a third dysentery. He managed to remain at work, but felt very ill and passed three stools a day.

In April 1922 he came to England and was re-investigated in London. As the result of various examinations, and particularly on the strength of the presence of fatty globules, fatty acids, and meat fibres in the stools, he was regarded as having pancreatic disease. He made no improvement with pancreatised food or pancreatin. In August 1922, as he was making no headway, an exploratory laparotomy was performed by Mr. Cecil Joll. A condition of *tabes mesenterica* was revealed, and, as in the other case, the lacteals were seen to be enormously distended.

On admission in January 1923 for further observation patient was terribly emaciated, his weight having fallen from ten to seven stone in two years. The abdomen was greatly distended and tympanitic. He was suffering from an abnormal hunger and thirst. He expressed himself as fond of fats, cream, butter, and savoury jellies.

With a fat-free diet, liberal fluids, and pituitary injections to control the meteorism, some temporary improvement was achieved, but it was only too apparent that in addition to lacteal obstruction from glandular disease the patient was also suffering from tuberculous ulceration of the intestine, and he did not long survive.

In this case, as in Case No. 1, the fallacy arose of supposing that fat and meat fibres in the stools must necessarily indicate pancreatic deficiency. The fat in each case was due to faulty absorption from obstruction of the lacteals, and the meat fibres were merely an expression of the diarrhoea.

Although chronic or intermittent diarrhoea with light-coloured stools is a well-recognised symptom of mesenteric glandular tuberculosis (four such cases—two adults and two children—have come to my notice in the past six months), manifestations of the character and severity seen in Cases 1 and 2 must, I think, be rare.

So similar are the main symptoms recorded in Case 1 to those recorded in cases of coeliac disease, that I would submit that the causal pathology of coeliac disease cannot be regarded as fully investigated until it has been demonstrated at operation or post-mortem that there is, or is not, some obstructive lesion in the lacteal system or the thoracic duct. The lesion is

most likely to involve the mesenteric glands. In none of the post-mortem examinations in cases of coeliac disease referred to by Still<sup>5</sup> and by Miller<sup>6</sup> is any specific mention made of the state of the lacteals. The fact that the lacteals may be seen to be distended at operation on a patient taking a normal diet does not necessarily imply that they should remain visibly enlarged after death in patients who have been on a low diet and have died of some terminal infection. The lacteals were not stated to be so distended after death in the case reported by Gull, the clinical description of which closely conforms with the description of Case 2. Evidence of tuberculosis has been consistently lacking in fatal cases of coeliac disease, but lymphatic obstruction need not necessarily be the result of tuberculosis. In fatal cases of fatty diarrhoea reported by Poynton and Paterson<sup>8</sup> and by Whipple<sup>9</sup> there was gross non-tuberculous enlargement of the mesenteric glands, and in Whipple's case the glands, which were fibrotic, and the intestinal villi were packed with deposits of neutral fats and fatty acids.

Gee,<sup>10</sup> in his original account, apparently draws no distinction between the coeliac disease of infants and those tropical cases of fatty diarrhoea which we now classify as Sprue. Manson-Bahr,<sup>11</sup> in describing the morbid changes found in sprue, says, "The mesenteric glands are generally large and pigmented, perhaps fibrotic." He also mentions the occurrence of tetany in chronic cases. Recently attention has been drawn by T. H. Jamieson<sup>12</sup> to the good results obtained with a fat-free dietary in sprue, while H. H. Scott<sup>13</sup> has demonstrated calcium deficiency, and commends the use of calcium lactate and parathyroid. It seems highly probable that the tetany and calcium deficiency which occur in some cases both of coeliac disease and sprue, may be connected with the excessive excretion of calcium soaps, as in Case 1.

Miller, who is responsible for several important contributions to the study of coeliac disease, claims that there is not sufficient evidence to indicate that the failure to absorb fats is due to any lesion of the intestinal mucosa. He concludes<sup>6</sup> "that coeliac disease is independent of organic changes and thus must be due to a digestive fault (probably a defective action of the bile on fat-absorption)." That such a gross derangement can depend upon "a defective action of bile on fat-absorption" alone, when there is no evidence forthcoming of hepatic, biliary, or pancreatic disease, seems to me to be an untenable hypothesis.

To replace it I would therefore put forward the suggestion that *the inability to absorb fats in coeliac disease, and the atten-*

*dant complications, such as infantilism and tetany, can best be accounted for by an obstructive lesion (probably infective in origin, as the disease is acquired and not congenital) of some part or parts of the lacteal tree.* The severity of the condition probably bears some relation to the amount of the obstruction, and in Miller's non-diarrhœic cases<sup>7</sup> it would be reasonable to suppose that there is less involvement of the mesenteric glands than in the fully developed type of the disease. On this hypothesis also the slow recoveries from cœliac disease might be held to be due in part to the establishment of a collateral lymphatic circulation, and the generally prompt improvement on a fat-free dietary to relief from overpressure of chyle in the already choked lymphatic tributaries.

The following case of infantilism and late rickets displayed features strongly reminiscent of cœliac infantilism. The blood-calcium was deficient, and although diarrhœa was only occasional there was excess of fat in the fæces. The patient also showed clinical and radiographic evidences of tuberculosis, and I consequently suggested a diagnosis of old mesenteric glandular tuberculosis causing faulty fat-absorption, and so contributing to the retardation of growth and the ricketty bony changes.

*Case 3.*—A girl aged fifteen was admitted for "arrest of growth, deformities, and intestinal troubles."

At the age of three and a half years she had a febrile attack accompanied by the passage of loose grey motions. These attacks have recurred three or four times a year ever since. At ten years she only weighed 4 st. 5 lbs. Her appetite has always been poor, and she will not touch milk. The stools have varied in character from day to day, but except in the attacks there is no diarrhœa. Patient is small, and in bulk and stature resembles a child of about eight or nine. She is "old-fashioned" in her expression and behaviour. There is great enlargement of the ends of the long bones, and a severe condition of knock-knee. Weight 4 st. 11 lb. The temperature chart shows slight daily excursions above the normal.

On a Schmidt's diet the stools showed no excess of meat fibres and no fat globules, but some excess of soap crystals. On an ordinary full diet a loose stool was passed which showed a few fatty globules, and some excess of soap crystals.

Dr. J. H. Ryffel reported quantitatively on the dried fæces and blood-calcium as follows:—

" Total fatty acid and fat	.	.	.	29.54 per cent.
Fatty acid as soaps	.	.	.	15.62 "
Free fatty acid and neutral fat	.	.	.	13.92 "

These figures are distinctly high but bear normal relationships.

“ The serum-calcium was definitely though slightly low as regards total calcium and more so for precipitable calcium.

Calcium in ash of serum, 8.9 mg. per 100 c.c. (Normal 9.2–10.0.)

Calcium precipitated directly by oxalate, 7.9 mg. per 100 c.c. (Normal 0.8–0.5 less than Ca. in ash.) ”

“ Radiograms of the chest showed considerable enlargement of root shadows and shadows in the right upper lobe suggestive of phthisis.” (Mr. P. J. Briggs.)

A fat-free diet was prescribed and, in view of a low curve of gastric acidity, dilute hydrochloric acid m. xxx three times a day with meals. Ten months later the patient's doctor (Dr. C. Ewbank Lansdown) reported :—“ Up to present date she has steadily improved on the treatment recommended. . . . There have been only two or three slight set-backs. There has been no return of the grey slatey-coloured motions. She has gained 1 st. 8 lb. in weight. The rickets have to all intents and purposes disappeared. Muscular development has very much improved. She is not like the same child, being happy and cheerful and developing.”

It is not easy to collect information as to the comparative frequency of pancreatic disease and disease of the absorbent system as a cause of fatty diarrhoea. During and since the period in which the three cases described came under observation, and among a considerable series of cases of chronic diarrhoea from all causes, I have seen no case of pancreatic diarrhoea either in the course of hospital or private practice. It would seem reasonable to suggest that the importance of pancreatic disease as a cause of fatty diarrhoea has been overstressed, while that of disease involving the absorbing apparatus has not hitherto received sufficient attention. Furthermore, it is probable that some cases of fatty stools attributed to pancreatic disease, but unconfirmed, have really been due to other causes.

Garrod,<sup>14</sup> in his Schorstein Lecture on pancreatic disease, says :—

“ In cases with no gross steatorrhoea the microscope may show abundant fat globules and many acicular crystals of fatty acids. Moreover, the large bulk of the fatty stools may arrest attention, and in some cases they are justly described as elephantine.”

Such a description might well be applied to the stools in cases of fatty diarrhoea due to obstruction of the lacteals (*vide* Case 1).



## CONCLUSIONS

1. The passage of copious, greasy, pale, offensive stools, containing an excess of fatty matters, chiefly as split fats, and also (in virtue of the diarrhoea) undigested meat-fibres, may result from obstruction of the lacteals by tuberculous mesenteric glands.

2. Tetany, and possibly in children late rickets, may occur in this condition. Both manifestations are probably related to the calcium deficiency caused by the excessive excretion of calcium in the form of soaps.

3. Similar stools, a similar abdominal enlargement and tetany are also recorded in the coeliac affection and in sprue. It is not improbable that an inflammatory occlusion of some part of the lacteal system is responsible for the common symptoms in these diseases.

4. Whether for combating the main or subsidiary symptoms rigid fat restriction should play an important part in the treatment of such conditions so long as the stools continue to give an indication of mal-absorption of fat.

I am greatly indebted to Dr. A. F. Hurst for permission to report upon the three cases referred to above.

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# ANISOCYTOSIS WITH SPECIAL REFERENCE TO PERNICIOUS ANÆMIA

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IN this account, by anisocytosis is meant the variation in size of the red cell diameter. The method by which the diameters of the red cells are measured and the degree of anisocytosis

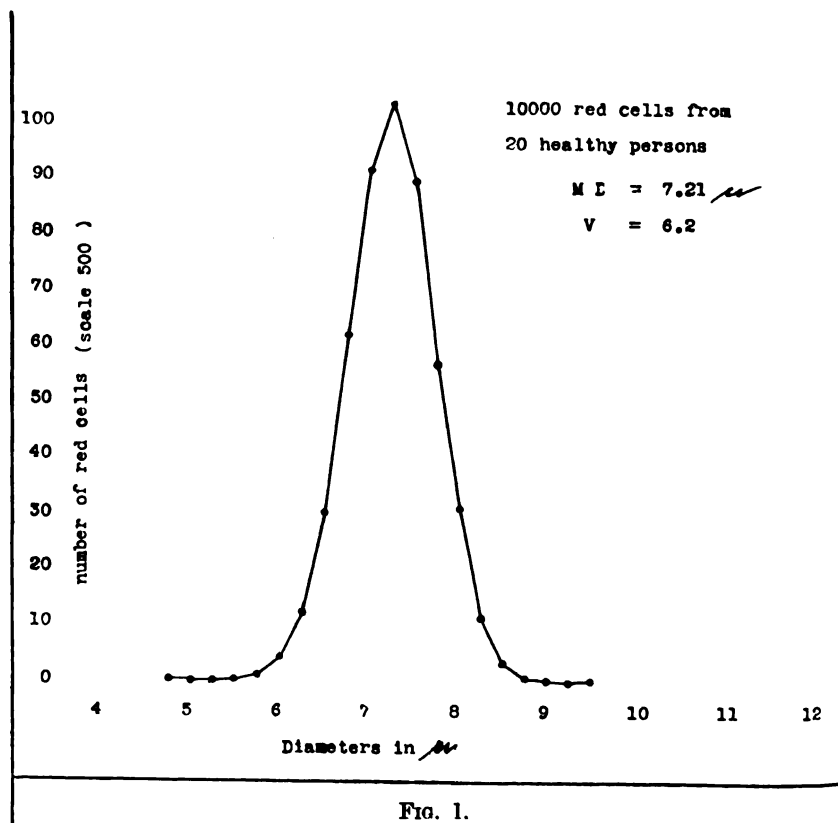


FIG. 1.

is estimated has been described by me in a previous paper (1920<sup>1</sup>) and need not be detailed here. The degree of anisocytosis or coefficient of variation is the standard deviation expressed as a percentage of the mean diameter, and forms a measure of the variability which is independent of the units in which the measurements have been made.

In consideration of the fact that there is diurnal variation in the sizes of the red cell diameters (1920<sup>1</sup>), all specimens of blood were taken in the forenoon. Five hundred cells were measured in every case.

### HEALTHY PERSONS

In healthy persons the diameters of the red cells vary from  $4.75\mu$  to  $9.50\mu$ . Taking samples of 500 cells, the average mean

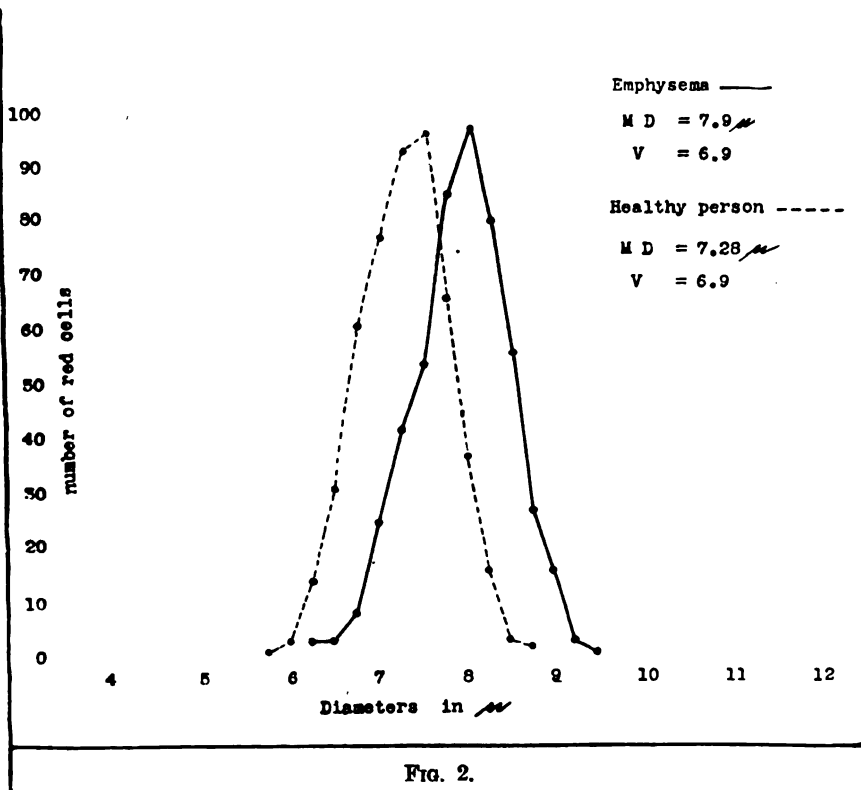


FIG. 2.

diameter of the red cells from twenty persons was  $7.24\mu$ , the average coefficient of variation or degree of anisocytosis was 6.4 per cent.

The curves of distribution of these cell diameters are symmetrical in type, and all the twenty curves show a strong similarity among themselves. They all "fit" well with their respective "normal" or binomial curves (1922<sup>3</sup>).

Fig. 1 shows the symmetrical curve of 10,000 red cell diameters obtained from twenty healthy persons.

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### EMPHYSEMA

In persons suffering from emphysema the diameters of the red cells vary from  $5.25\mu$  to  $9.75\mu$ . Taking samples of 500 cells, the average mean diameter of the red cells from twenty-two cases was  $7.69\mu$  or about half a  $\mu$  greater than healthy cells. The average variability was 7.06 per cent., only slightly greater than in health.

The curves of distribution of these cell diameters are moved

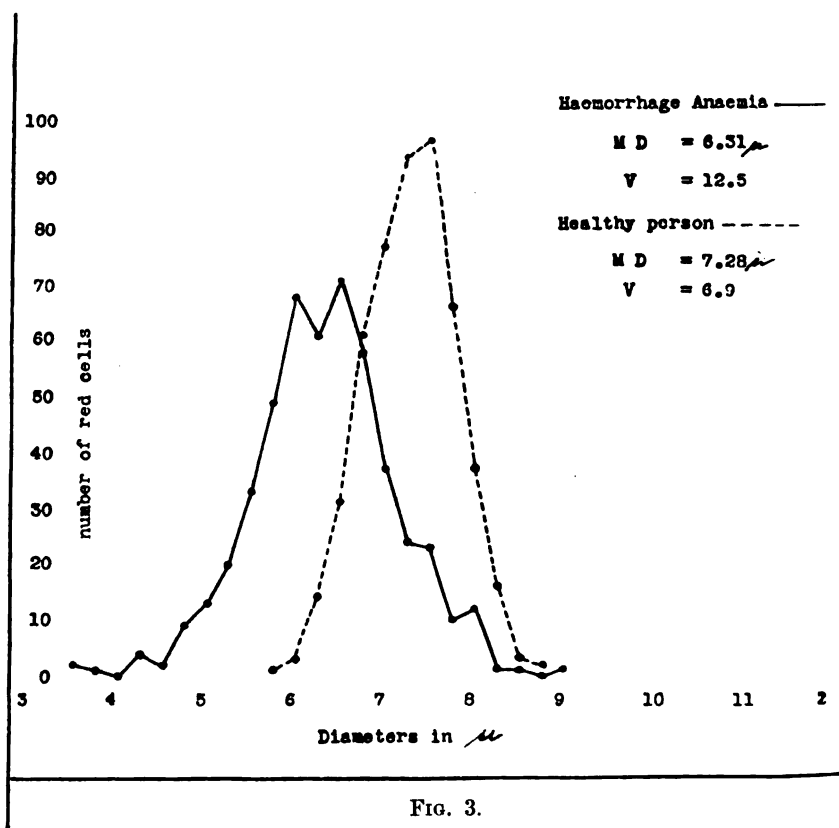


FIG. 3.

to the right of the healthy curve (Fig. 2); they are symmetrical in type, and like the healthy curves show great similarity among themselves, and they all "fit" fairly well with their respective "normal" curves. In other words, all the cells in a sample are proportionally increased in size, being associated, as I have suggested (1921<sup>2</sup>), with an increased quantity of  $\text{CO}_2$  in the blood, in spite of its normal reaction, and which must have a special swelling action on the corpuscles out of proportion to its acidity, analogous to its action on the respiratory centre.

## HÆMORRHAGE ANÆMIA

In the blood of persons suffering from anæmia following hæmorrhage the diameters of the red cells vary from  $3.50\mu$  to  $11.0\mu$ . Taking samples of 500 cells, the average mean diameter of the red cells from ten cases was  $6.879\mu$ , the average variability was 9.98 per cent.

The curves of distribution of these cell diameters are moved to the left of the healthy curve (Fig. 3). They are usually of less symmetrical type, show less similarity among themselves, and do not "fit" so well with their respective "normal" curves.

In these cases it seems legitimate to assume that there are two classes of cells: (1) small cells newly formed by over-stimulation of the bone marrow on account of the anæmia caused by the loss of blood; (2) normal-sized cells. The dominance of one kind of cell would be expressed by a more or less symmetrical curve. A low mean diameter with such a curve type would represent the production of small cells by over-stimulation of the bone marrow and would conceivably occur after a severe hæmorrhage. A symmetrical curve with only slightly, or not at all, diminished mean diameter of red cells would indicate the continued production of normal-sized cells and might be expected after slight hæmorrhage. Asymmetrical curves would suggest intermediate conditions and might be expected during convalescence. In other words, the relative share taken by these two classes of cells would depend on the amount of the hæmorrhage, on the period after the cessation of the hæmorrhage at which the examination was made, and also on the specific rate at which the individual was able to return to health.

It is, however, noteworthy that even in those cases where the mean diameter was not significantly different from that of healthy blood cells, the degree of anisocytosis was always greater than in health.

## POLYCYTHÆMIA

In the subjoined table are shown the measurements of six cases of polycythæmia. Two of these are cases of splenomegalic polycythæmia (Vaquez), and four are cases of congenital heart disease. These two classes of the condition present an interesting contrast.

In splenomegalic polycythæmia the bone marrow is senselessly producing red cells. The condition may be regarded as a benign tumour of the blood. To enable the heart to overcome the increased work due to the greater viscosity of the blood, the blood volume is increased. The morbid activity of the

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bone marrow is demonstrated by the presence of nucleated and other immature forms of red cells in the circulating blood. In Case 1 a sample of blood, having 9,920,000 red cells per cmm., and Hb per cent. of 151, was centrifuged. The corpuscular volume was 78.6 per cent. A sample of healthy blood with 4,507,000 red cells per cmm. was simultaneously centrifuged and had a corpuscular volume of 42.3 per cent.

If the red cells of the polycythæmia patient had been of normal size the volume of his red cells would have been  $\frac{42.3 \times 9.92}{4.507} = 98$  per cent., in which case the blood would have

been almost too thick to circulate. But the mean diameter of the red cells was only  $6.8\mu$ , and the variability 9.5 per cent.

The blood of this patient was examined thirty times in the course of five months. The mean diameters were always low, ranging from  $6.6\mu$  to  $7.0\mu$ , and were not appreciably affected by venesection. The curves of distribution were moved to the left of the healthy curve, they were symmetrical in type, and generally fitted well with their respective "normal" curves. The average variability was 9.5 per cent.

In Case 2 the corpuscular volume of the blood was not estimated. On two examinations the red cells were over 8 millions per cmm., the Hb. over 150 per cent., the mean diameter of the red cells  $6.86\mu$ , and the variability 9.1 per cent. These figures are very similar to those of the preceding case. The blood films exhibited nucleated red cells and other immature forms pointing to abnormal bone marrow activity. In neither of these cases was there any noticeable cyanosis.

Referring to a case of splenomegalic polycythæmia without cyanosis, Parkes Weber <sup>4</sup> mentions the "abnormal variation in size of the erythrocytes," which with the other blood findings "all point to excessive functional activity of the bone marrow." The mean diameter of the red cells was not estimated.

The four cases of polycythæmia associated with congenital heart disease showed no diminution in the mean diameter of the red cells, though with the exception of Case 4, the variability was raised above that of healthy blood cells.

TABLE I

Case.	Red cells, in millions per cmm.	Hb%.	Mean diameter, in $\mu$ .	Variability %.	Remarks.
1	9.92	151	6.83	9.5	splenomegalic
2	8.34	158	6.86	9.1	"
3	8.80	158	7.23	8.2	congenital heart
4	6.20	108	7.60	6.1	"
5	9.73	132	7.24	8.1	"
6	7.97	140	7.31	7.9	"

In these cases of polycythæmia, associated with congenital heart disease, the bone marrow is over-stimulated to produce more red cells by the deficient oxygenation of the blood resulting from the cardiac deformity. Accordingly it would be right to expect small red cells, which apparently is not the case. The immediate suggestion is that the cells are really small, but owing to the deficient aeration of the lungs and probable increase of  $\text{CO}_2$  in the alveoli the cells have become swollen in the same manner as the red cells in emphysema cases. This explanation, however, seems to be negatived by a series of observations I have made on the red cell diameters of fifteen cases of cardiac disease all suffering from varying degrees of heart failure associated with dyspnoea, cyanosis and venous congestion (1921<sup>2</sup>). The average mean diameter of the red cells in these cases was  $7.22\mu$ , or not different from that of healthy persons. The average variability was 7.07 per cent. Unfortunately complete blood examinations were not made of these cardiac cases. Clinically, however, many were obviously severely anæmic, and to me it seems a legitimate assumption that more or less anæmia was present in all of them, and in consequence the red cells were probably really small, but owing to the prevailing pulmonary distress and presumable increase of  $\text{CO}_2$  in the alveolar air, the cells became swollen and gave relatively increased mean diameters.

#### PERNICIOUS ANÆMIA

In pernicious anæmia the diameters of the red cells vary from  $3.75\mu$  to  $13.0\mu$ . Taking samples of 500 cells, the average mean red cell diameter of 68 observations was  $8.81\mu$ , or over  $1\mu$  greater than the average mean diameter of healthy red cells. The average variability was 12.15 per cent., or about twice that of healthy cells.

The curves of distribution of the red cell diameters lie to the right of the healthy curve (Fig. 4); they show marked dissimilarity among themselves and are often extremely asymmetrical and grotesque. These curves fit badly with their respective "normal" curves; they are frequently poly-modal, and have the appearance of being composite curves formed by two or more kinds of cells included in a heterogeneous cell population. This suggestion is compatible with the assumption that the blood of pernicious anæmia contains three classes of red cells: (1) large cells arising from some abnormal excitation of the bone marrow, probably only of some portions, even quite small portions, of the bone marrow. These cells may be regarded as constituting the "pernicious" element. It has



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been suggested that this process is possibly analogous to the production of a malignant growth. (2) Normal-sized cells resulting from the normal stimulation of the healthy portions of the bone marrow. (3) Small cells resulting from the extra stimulation of the remaining portions of the bone marrow as the result of the anæmia caused by the abnormal destruction of red cells. These cells may be regarded as constituting the "anæmia" element. I suggest a practical name for this condition is "Megalocytic anæmia."

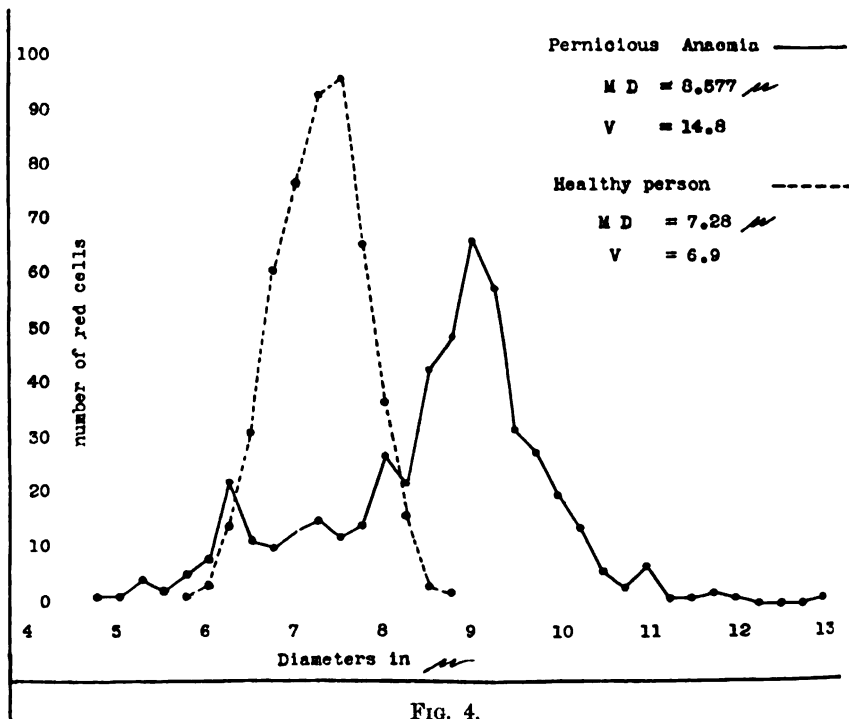


FIG. 4.

In a previous paper (1922<sup>3</sup>) I considered single observations of the blood of twenty cases of pernicious anæmia, and from these I concluded there was no correlation between the hæmoglobin percentage and the mean red cell diameter, nor between the hæmoglobin percentage and the variability, and I suggested that this want of correlation is due to a variable amount of hæmoglobin in the individual red cells, and that whereas in health the amount of hæmoglobin is proportional to the size of the cell, in unhealthy cells this relation does not hold. It is common knowledge that the red cells of anæmic blood stain unequally with eosin, and polychromatic red cells, which are

constantly present in these cases, very probably contain less hæmoglobin than the normal cells of the same size.

In the present account of 68 observations I find that although there is no correlation between the mean diameter of the red cells and the number of the red cells per cmm. (Fig. 8), or between the mean diameter of the red cells and the hæmoglobin percentage (Fig. 9), there is a very definite correlation between the variability (degree of anisocytosis) and the number of red cells per cmm. (Fig. 5), and also between the variability and the

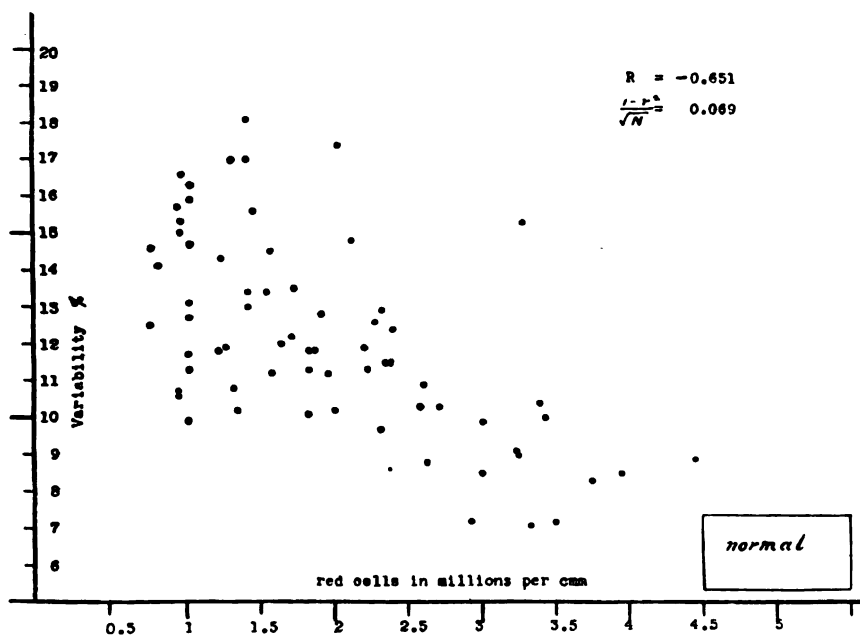


FIG. 5.

hæmoglobin percentage (Fig. 6), in the sense that the variability is in inverse relation to the number of cells and hæmoglobin percentage, or in other words the degree of anisocytosis varies directly with the degree of anæmia. It also appears that there is only a doubtful correlation between the variability and the mean diameter of the red cells.

In Fig. 5 I have plotted out the 68 red cell counts according to their respective coefficients of variation. In the right-hand corner of the chart are shown the corresponding relations and limits for healthy red cells. It is at once seen that there is probably some correlation between the number of red cells per cmm. and the variability of the red cell diameter. On calculating the coefficient of correlation (Yule, pp. 183-186<sup>5</sup>) I found

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$R = -0.651$ , and the probable error (Karl Pearson<sup>6</sup>) of this value is 0.069, so that  $R$  is over nine times the probable error, or in other words the coefficient of correlation  $-0.651$  is significant and may be regarded as a good correlation. It expresses the fact that the greater the variability is the fewer are the number of red cells.

In (Fig. 6) is a similar plotting of hæmoglobin percentages and their respective red cell diameter variabilities. In the right-hand corner are the corresponding relations and limits for healthy blood. Here again a definite correlation is suggested.

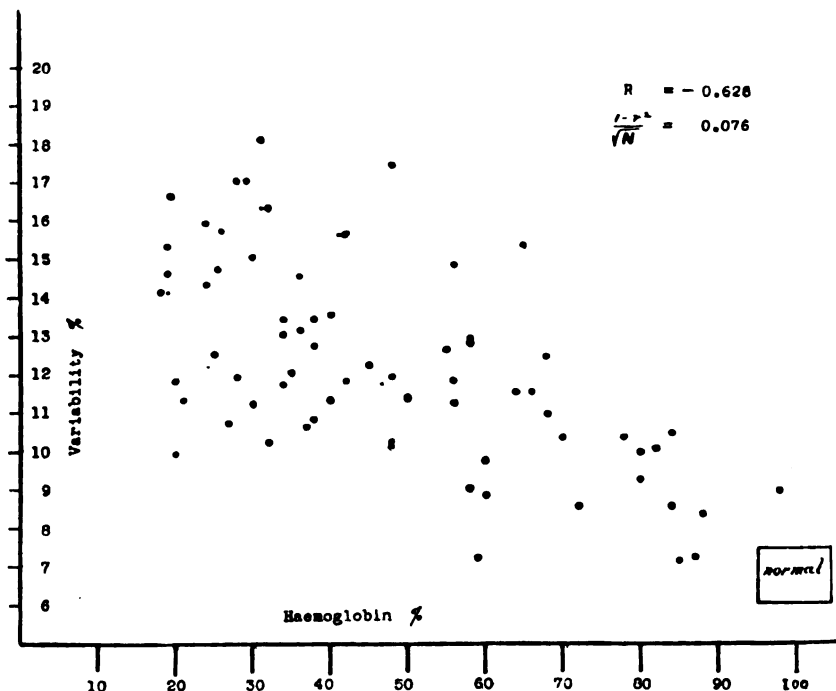


FIG. 6.

On calculation it is found that  $R = -0.628$ , and the probable error is 0.076, so that  $R$  is over eight times the probable error, and may be regarded as a significant and good correlation, expressing the fact that the greater the variability the lower is the hæmoglobin percentage.

Taken together these two charts seem to establish conclusively that the degree of anisocytosis varies directly with the degree of anæmia.

Fig. 7 shows a similar plotting of mean diameters and their respective variabilities. The presence of any correlation is only doubtfully suggested. On calculation  $R = -0.27$  with

a probable error of 0.112, so that  $R$  is only just over twice the probable error, and therefore on the three times rule it cannot be regarded as significant.

Fig. 8 is a plotting of mean diameters and their respective red cell counts. There is obviously no correlation, and on calculation  $R = 0.115$  with a probable error of 0.119. Similarly in Fig. 9, showing plottings of mean diameters and their respective hæmoglobin percentages, there is obviously no correlation.  $R = 0.126$  and the probable error is 0.119.

The absence of correlation in these last two charts establishes

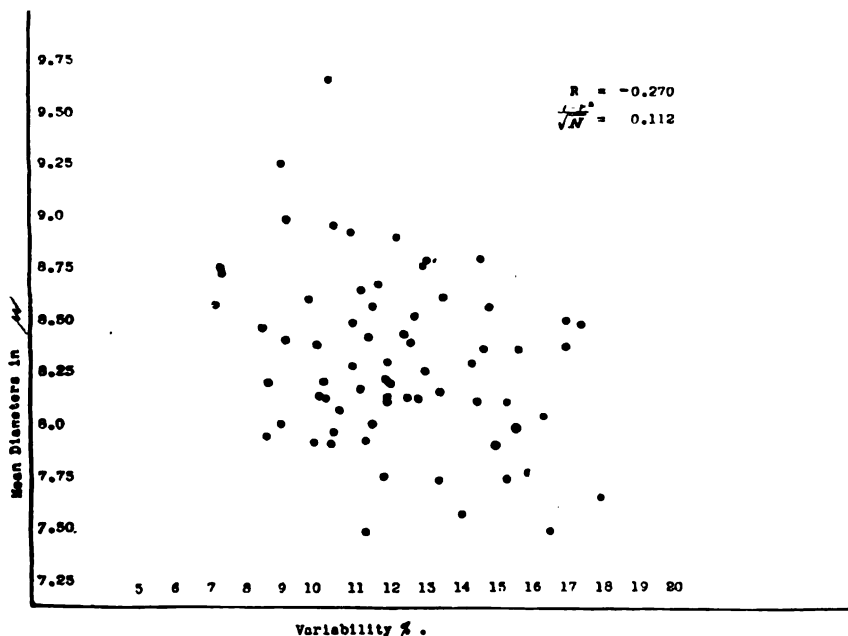


FIG. 7.

a remarkable characteristic of the blood in this condition, viz. that the red cell diameters are independent of the severity of the anæmia. This is also exhibited in Table II, in which it appears that the large mean diameter of the red cell persists throughout the illness, and even when the patient is apparently convalescent. In Case 4, when first examined by me, the red cell count was 4,440,000 per cmm., Hb per cent. 98, and colour index 1.1. From these values it would have been difficult to diagnose "pernicious anæmia." Measurement of the red cell diameters gave a mean of  $8.02\mu$ , with a variability of 8.9 per cent. Five months later the patient was readmitted to hospital, and a blood examination then gave red cells 2,620,000, Hb per cent. 78, colour index 1.5. The mean diameter of the

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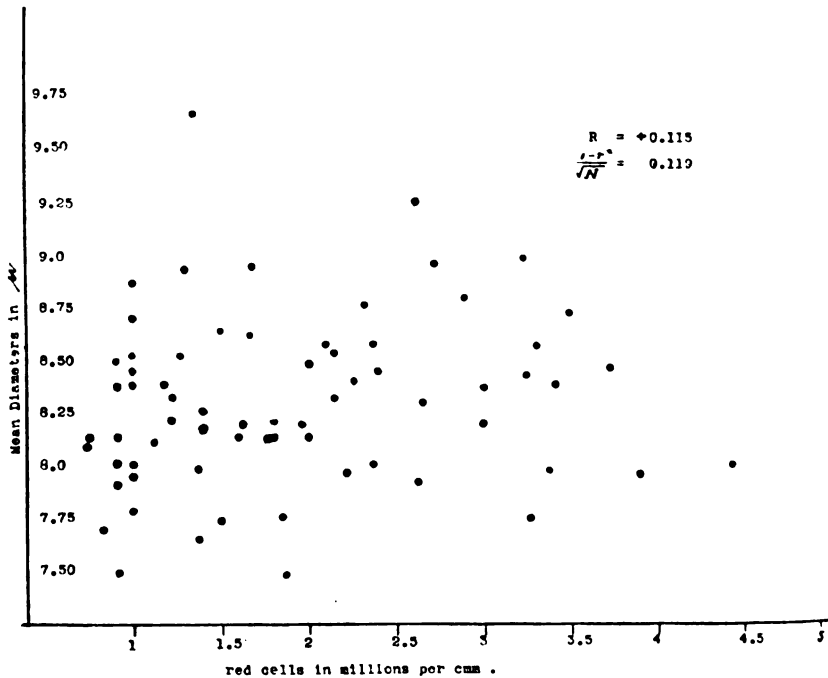


FIG. 8.

red cells was 7.91, or practically unchanged. The variability had risen to 10.3 per cent. in association with the increased anæmia.

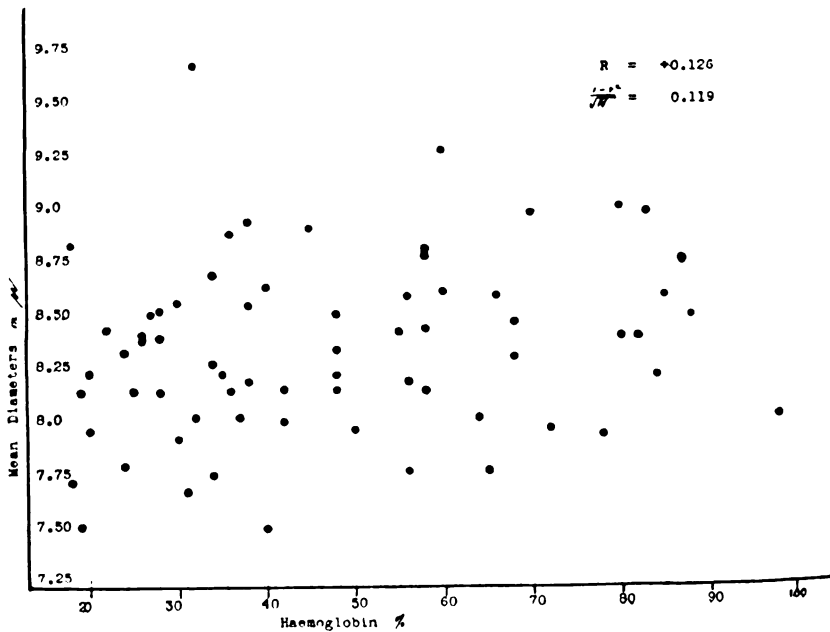


FIG. 9.

TABLE II

Case.	Date.	Red cells in millions per cmm.	Hb%.	Mean red cell diameter.	Variability %.	
1	12 xi. 21	1.37	28	8.369	17.08	
	3 v. 22	2.29	60	8.585	9.7	
	13 xii. 22	1.06	38	8.533	12.7	
	16 i. 23	1.40	38	8.172	13.4	
	31 i. 23	1.40	34	8.259	13.0	
	14 ii. 23	1.26	28	8.118	11.9	
2	27 x. 22	1.59	36	8.133	14.5	
	6 xii. 22	2.00	48	8.478	17.4	
	22 xii. 22	2.66	68	8.290	10.9	
	8 i. 23	3.06	80	8.365	9.9	
	31 i. 23	3.00	84	8.190	8.5	
	28 ii. 23	3.90	72	7.940	8.5	
3	6 ii. 22	2.15	48	8.314	11.9	
	13 ix. 22	2.38	66	8.570	11.5	
	17 i. 23	3.39	84	7.965	10.4	
4	6 x. 21	4.44	98	8.022	8.9	
	28 iii. 22	2.62	78	7.913	10.3	
	22 iv. 22	2.02	48	8.131	10.2	
5	22 viii. 22	0.75	25	8.137	12.5	
	31 viii. 22	0.93	30	7.915	15.0	{ 2 days after transfusion.
	16 ix. 22	1.03	36	8.856	13.1	
	29 ix. 22	1.31	38	8.919	10.8	
	12 x. 22	1.04	34	8.685	11.7	
	1 xi. 22	0.93	37	8.093	10.6	
	20 xi. 22	0.93	27	8.487	10.7	{ 2 days before death.
6	31 i. 21	3.25	58	8.418	9.0	
	26 iv. 22	1.21	24	8.310	14.3	
	23 v. 22	0.90	26	8.363	15.7	
7	16 xi. 22	2.28	55	8.408	12.6	
	27 xi. 22	2.40	68	8.440	12.4	
	4 xii. 22	2.36	64	8.036	11.5	
	13 xii. 22	1.78	58	8.124	12.8	
	20 xii. 22	1.94	56	8.176	11.2	
	27 xii. 22	1.85	56	7.751	11.8	
8	20 ii. 22	1.37	31	7.650	18.18	
	29 xi. 22	2.10	56	8.577	14.8	
9	16 ix. 22	1.82	48	8.198	10.1	
	11 x. 22	1.82	42	8.133	11.8	
	27 xii. 22	1.53	34	7.737	13.4	
10	23 x. 22	3.27	65	7.748	15.3	
	30 x. 22	1.04	24	7.787	15.9	
	9 xi. 22	0.93	19	8.125	15.3	
11	11 x. 23	1.34	32	9.673	10.2	
	24 x. 23	2.63	60	9.250	8.8	
	21 xi. 23	2.90	58	8.748	7.2	
12	19 vii. 22	3.30	85	8.572	7.1	
	24 x. 22	3.50	87	8.719	7.2	
	20 iii. 22	3.74	88	8.456	8.3	
13	29 xi. 22	2.30	58	8.764	12.9	
	31 i. 23	3.41	82	8.374	10.0	
	14 iii. 23	3.24	80	8.982	9.1	

Table II comprises measurements from thirteen cases which I have examined on several occasions during the course of the disease. It also exhibits pretty constantly the correlation demonstrated above between the variability and the degree of anæmia. In Case 1 a rise in the red cell count of 900,000 per cmm. and Hb per cent. of 82 is accompanied by a fall in the variability of 7·8 per cent., and a subsequent fall in the red cell count of 1,280,000 and Hb per cent. of 22 was associated with a rise of 8 per cent. in variability. In Case 2 a rise in red cell count of 1,900,000 per cmm., and Hb per cent. of 24 is accompanied by a fall in variability of 6·9 per cent. In Case 6 a fall in the red cell count from 3,250,000 to 0,906,000 per cmm., and Hb per cent. from 58 to 26 is associated with a rise in variability from 9 per cent. to 15·9 per cent. The same principle holds in most of the other cases, with the marked exception of Case 10, where the variability remains constant in spite of a very great alteration in the degree of anæmia.

In Case 5 the examination made two days after transfusion showed, as might be expected, a lowered mean diameter of the red cells and an increased variability owing to the introduction of normal-sized cells.

#### SUMMARY

The outstanding features of the blood in cases of "pernicious anæmia" are :

(1) Megalocytosis, or raised mean diameter of the red cells over that of healthy red cells.

(2) High degree of anisocytosis, which varies directly with the degree of anæmia.

The large mean diameter of the red cells is independent of the degree of anæmia, and persists throughout the course of the disease.

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# THE IMPORTANCE OF ESTIMATING CHLORIDES IN THE FRACTIONAL TEST MEAL SAMPLES, AND SOME EXPERIMENTS WITH THE DUO- DENAL TUBE

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IN a series of fractional test meals on sixty healthy medical students, including four women, the shape of the curve of acidity seemed to depend on three factors. These are the amount of gastric juice secreted, the rate of emptying of the meal, and the amount of neutralisation of the acidity which took place in the stomach.

Some food generally leaves the stomach almost at once, but the rate of emptying depends on the extent of the relaxation of the pyloric sphincter, as well as on the time at which this starts and the frequency with which it takes place. If the neutralisation is due to the regurgitation of pancreatic juice, this also depends on the relaxation of the sphincter, and the passive regurgitation from the duodenum probably requires greater relaxation of the sphincter than the onward passage of the food which is driven forward by the peristaltic waves.

The importance of the regurgitation of bile and pancreatic juice in this connection was first emphasised by Boldyreff.<sup>1</sup> It was discussed by Bennett and Ryle<sup>2</sup> and has since been very carefully investigated by Bolton and Goodhart.<sup>3, 4</sup> The latter pointed out that the curve of total chlorides is a better measure of gastric secretion than the curve of acidity, for much or little of the acid may have been neutralised.

In various diseases of the stomach and in some healthy students Bolton and Goodhart estimated the total chlorides as a measure of gastric secretion and the inorganic chlorides as a measure of the amount of regurgitation from the duodenum, the curve of acidity as ordinarily found being roughly the difference between the two. Obviously this gives much more information about what is taking place than the ordinary test meal. For total and inorganic chlorides they ashed the samples,

\* This work was done during the tenure of the Hilda and Ronald Poulton Fellowship at Guy's Hospital.

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with and without the addition of soda, and then titrated by Volhard's method. As they say, this is a lengthy and laborious process to apply to the fractional meal as a routine.

### ESTIMATION OF CHLORIDES

It seemed to us that the same information might be obtained more easily. Ordinary titration does not give exactly the amount of acid in a gastric sample, because it depends on the hydrogen-ion concentration at which the indicator changes, the protein present acting as a buffer. By mixing gruel and known amounts of acid, the real significance of titration with dimethyl and with phenolphthalein can be worked out. If much acid and relatively little gruel are present in the mixture, the titration with dimethyl is found to give a very accurate measure of the acid. If little acid and much gruel are present, the acid is given fairly accurately by the mean of the two titrations. The experiments on which this is based and the degree of accuracy which may be expected are fully described in the appendix.

The next difficulty was to measure the chlorides without ashing. It is generally assumed that the direct Volhard method is not sufficiently accurate when protein is present. This can be tested in just the same way with mixtures of gruel, acid, and sodium chloride in known proportions. Provided the samples are filtered the total chlorides can be estimated with reasonable accuracy in this way, the average error being only 0.01 per cent. chloride. The inorganic chlorides can be measured by taking the difference between the total chloride and the hydrochloric acid when no other acid is present. This indirect way is not quite as accurate as the more usual way of ashing after adding sodium bicarbonate, but the average error is only 0.014 per cent. chloride.

For most purposes the curve of total chlorides, determined directly by Volhard's method, after filtration, but without ashing, is the best measure of the amount of gastric secretion. The area enclosed between this curve and a second one somewhere between the "total acid" and "free acid" curves, which generally run close and parallel to each other, is a good measure of the amount of alkali present. It has generally been assumed that this is derived from duodenal regurgitation.

### CURVE OF TOTAL CHLORIDES

In thirty students this was determined as well as the more usual titrations for acidity. The result is shown in Fig. 1.

A gives the average of all determinations, but B shows a more typical result and D an unusual curve.

The four striking things about the usual curve are—the high percentage of chloride in the resting juice; the close agreement

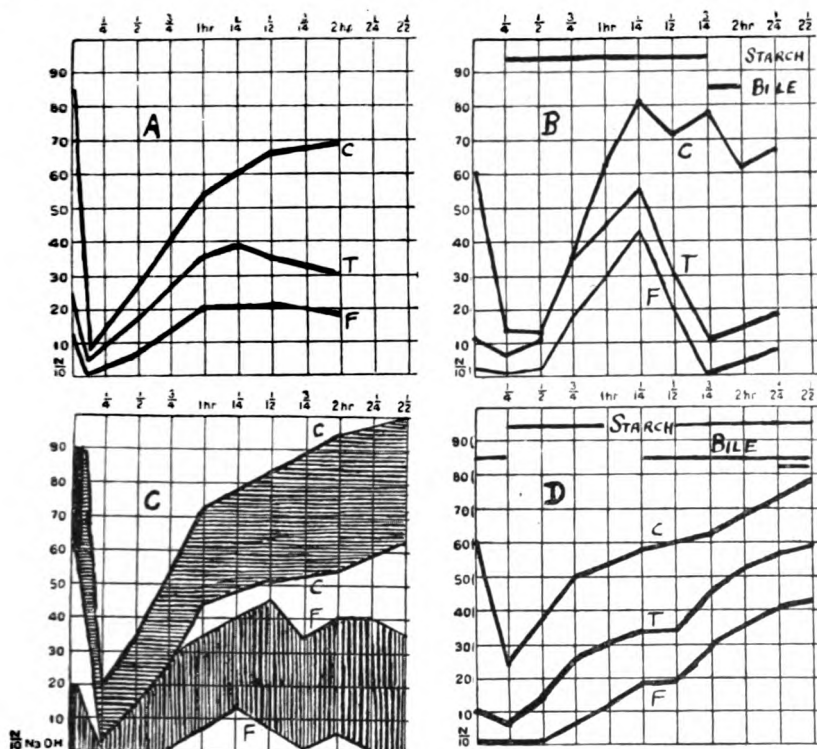


FIG. 1.

*Curves of total chloride, total acid and free acid after a gruel meal.*

In all charts in this paper the lowest line (F) shows free acid (di-methyl), the one above (T) total acid (phenolphthalein), and the third (C, when present) the total chloride. The presence of starch and bile is shown at the top of each chart. A double line shows a large amount of bile. The left-hand scale refers to c.c. of  $\frac{N}{10}$  NaOH used for titration of free and total acid. The chloride is referred to the same scale for comparison by calculating it as chloride instead of sodium chloride. 10 on this scale corresponds to 0.033 per cent.

A. Average result of all subjects.

B. Typical result.

C. The upper dark area includes the total chloride curve in eighty per cent. of these normal subjects. (The lower shaded area shows free acidity.)

D. Unusual type of chloride curve.

between the chloride and the acidity (expressed as HCl) during the early part of the meal; the divergence of these two later; and the fact that at the end of the meal the chloride is generally the same or a little higher than at the beginning. Compared

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to the curve for the free acid there is relative constancy in the chloride curve. C gives an idea of the range of variation, for in 80 per cent. of the subjects the curve for total chlorides lay within the upper shaded area.

In the resting juice the chloride is generally between 0.23 and 0.88 per cent.\* Relatively it is equally high whatever the acidity. For example, in half the subjects where the total acid averaged 0.04 the chloride was 0.26; and in the others the total acid averaged 0.14 and the chloride 0.86.

It is unlikely that the stomach secretes this large amount of chlorides; probably it is produced by the gastric HCl being neutralised in some way. This fact and the frequent presence of bile in the gastric juice after twelve hours without food suggest that normally, in the resting stomach, the pyloric sphincter is completely relaxed, and that it only closes when the stomach is filled with food, which is not yet ready to pass on to the duodenum.

As this resting juice is drawn off as completely as possible, the hydrochloric acid should be the only chloride in the early part of the test meal. In more than half of these cases the total acid and chloride curves are practically identical during the first three-quarters of an hour, though they diverge later. In only one quarter do they differ by more than 0.05 per cent. The greatest difference found is 0.11 per cent., and some of this may be due to incomplete withdrawal of the stomach contents before the meal: excluding the resting juice, only one subject, who was unusual in other ways as well, had any bile present during the first three-quarters of an hour. In the course of the meal the divergence of the total acid and chloride generally increases, and is sometimes very great.

### DIFFERENCES BETWEEN CURVES OF CHLORIDES AND OF ACIDITY

The curves may be grouped by their shape or by the maximum height which they reach. Bennett and Ryle found that 90 per cent. of their subjects showed a definite peak, and that of the remainder half were achlorhydric and half of the "climbing" type commonly found in ulceration near the pylorus. In this series only three-quarters of the subjects show a well-marked peak in their acid curves; about one-tenth are of the "climbing" type, the rest being intermediate between these ("plateau type").

\* Throughout this paper the chlorides are expressed as percentage of Cl instead of NaCl, so that they may be compared more readily with the percentage of HCl.

The curve of the total chlorides is quite different and a well-marked peak is unusual. One-quarter of these cases have a peak, but it is not well marked and frequently occurs just at the end when the stomach is nearly empty (Fig. 2B). In

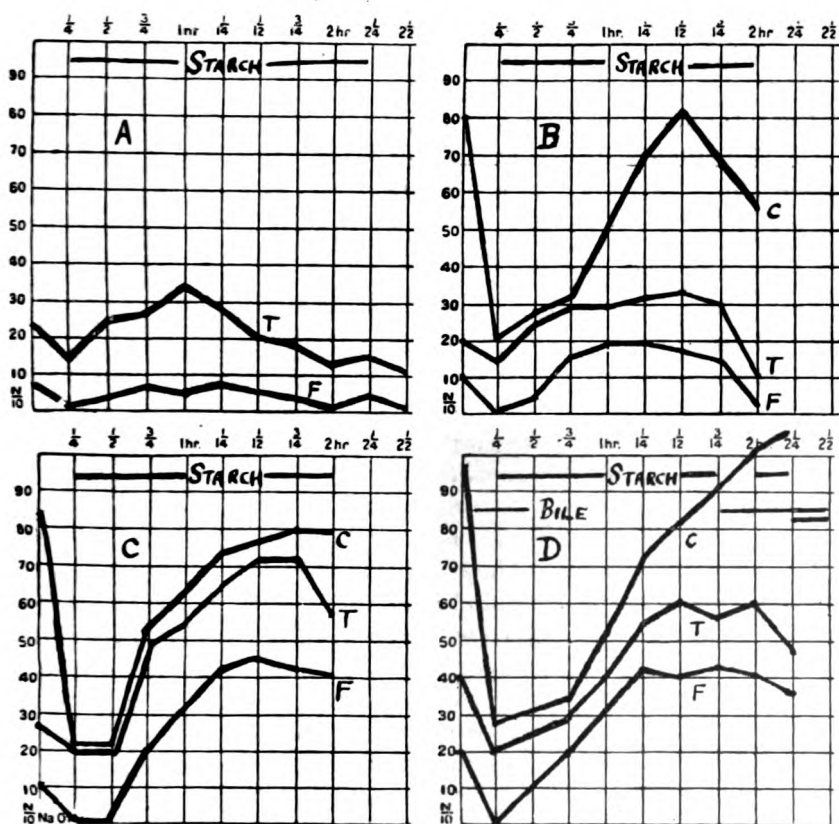


FIG. 2.

*Curves of total chloride (C), total acid (T) and free acid (A) after a gruel meal.*

A. Curves of acidity for M.B., suggesting deficient secretion.

B. Chloride curve for M.B., showing that apparent hypochlorhydria is due to excessive neutralisation (not associated with regurgitation of bile).

C. Unusual type of chloride curve with practically no neutralisation.

D. "Climbing" chloride curve showing neutralisation (associated with regurgitation of bile).

In A, B and C bile was absent throughout the meal.

one-half of the others the chloride curve is of the "climbing" (1D and 2D), and in the other half of the "plateau" type (e.g. 1B, 5C and 5E). As would be expected where the acid curve shows no peak, the chloride curve and therefore the actual secretion rises continuously; where the acid curve falls, the

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chloride curve remains level or continues to rise. In no subject does the chloride curve fall much more than is shown in 2B.

Fig. 2 also illustrates one advantage in estimating the total chlorides as well as the acidity. A and B are taken from the same subject. A, where the chlorides were not determined, suggests that the subject has rather deficient secretion, but B shows that it is quite normal in amount, and that the low acidity is due to the unusual extent of neutralisation. On both occasions bile is absent throughout the meal; we supposed at first that there was regurgitation of pancreatic juice without bile. There is the same significance in the examination of the resting juice, for a highly acid juice may not mean an abnormal secretion of acid, but simply that there is deficient regurgitation and neutralisation. It is also of importance in investigating cases of apparent achlorhydria.

What is the cause of the peak which generally occurs, and why is it sometimes absent? The most obvious explanation is that the pyloric sphincter, instead of opening momentarily at the end of a peristaltic wave to permit the passage of food, opens more widely when there is no increased pressure in the stomach, and so allows regurgitation of and neutralisation by an alkaline fluid, presumably pancreatic juice. The easiest way of testing this is by seeing when bile generally appears in the stomach, for it seems likely that in most cases bile and pancreatic juice will regurgitate together, or not at all.

Curiously enough in half the cases with a well-marked peak, bile is not present at any time; in one-quarter it appears just after starch has disappeared, when presumably the stomach is empty; and in only one-quarter does bile appear at such a time that it seems the probable cause of the fall in acid and the resulting peak.

Where there is no definite peak, the presence of bile generally seems to decide whether the curve is of the "climbing" or the "plateau" type.

The greatest divergence of the chloride and acid curves occurs at about the same time as the peak. If this were also the time when bile appeared, the explanation would be simple, but usually this is not so. As regurgitation of pancreatic juice without bile is so unexpected, other possible explanations must be thought of. Where the acid curve remains level the addition of chlorides without any further secretion of acid or neutralisation would be a sufficient explanation. These are not likely to come from the saliva, for special efforts were made to prevent it being swallowed, and in each case where it was examined its chloride content was extremely low. It is unlikely

that chloride is secreted in the gastric juice in any large amounts. Of course, chloride is known to be present in bile and pancreatic juice, but the cases now under consideration show no regurgitation of bile, and if pancreatic juice enters the stomach neutralisation takes place as well and the addition of chlorides becomes of less importance.

In any case where the acidity falls and the chlorides rise neutralisation must have taken place. The alkalinity of the saliva is much too low to be of much importance in this connection, and the pancreas seems to be the only likely source of a strongly alkaline fluid. It was in the hope of determining whether the regurgitation of pancreatic juice was the cause of this neutralisation, even in cases where bile was not present, that we experimented with the duodenal tube. It seemed that if continuous suction was exerted on the duodenal tube, so that everything entering the duodenum was at once sucked out, regurgitation would be prevented and the curves for chloride and for total acid should be practically the same. This did not turn out to be the case.

#### METHOD FOR OBTAINING CONTINUOUS SAMPLES FROM THE DUODENUM BY SUCTION

By swallowing two tubes so that one is in the stomach and the other in the duodenum, and sampling at short intervals, more information can be gained than by the ordinary test meal. Gastric samples are obtained in the usual way, and samples are withdrawn through the longer tube by suction with a water-pump, so that a continuous picture of events in the duodenum is seen. In this way it is possible to get results throwing light on various phases of normal digestion.

The details of the method are as follows. Two tubes are swallowed at the same time, and generally this is found to be as easy as swallowing one. When these have reached the stomach, the subject lies down on his right side and slowly pushes and swallows the longer tube to near its end. The resting juice is not drawn off because an empty stomach makes it easier for the tube to curl up, and delays its passage into the duodenum. Ten minutes later he is x-rayed and sometimes one tube is already in the duodenum. Enough barium sulphate emulsion to fill the tube is injected and its exact position made out. It is important to withdraw as much of this barium as possible, because with mucus it makes a sticky mess which easily blocks the holes.

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If the tube is not yet past the pylorus, the subject lies again on his right side for ten minutes. If it is seen to be curled up, it is drawn up until it is straight and is then swallowed

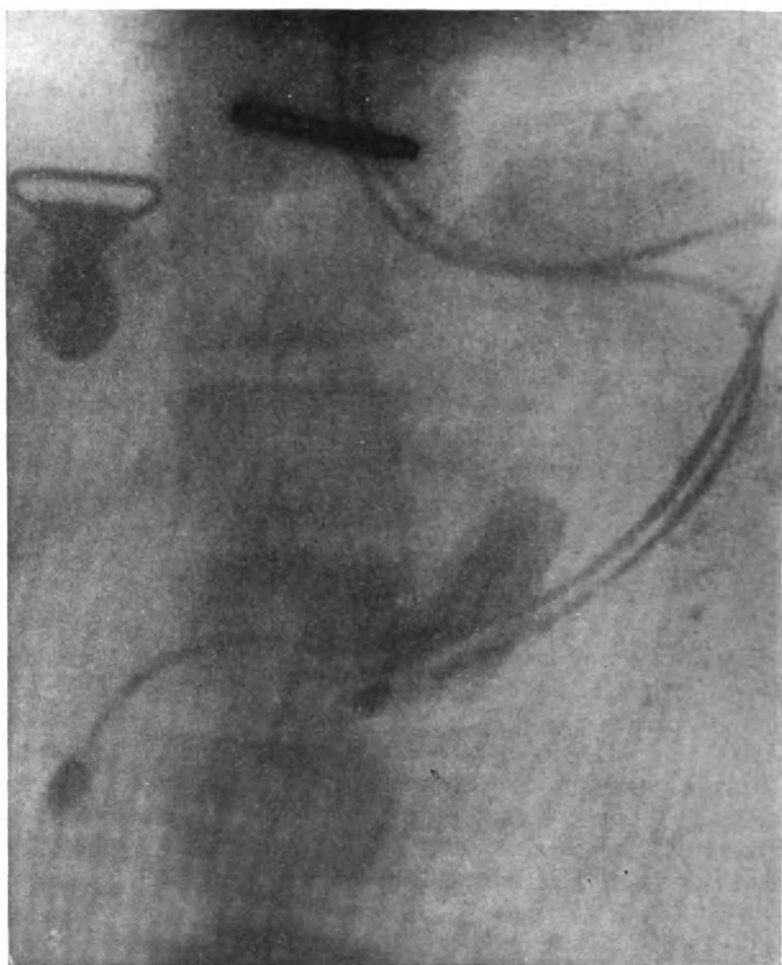


FIG. 3.

*Radiogram showing one tube in the stomach near the pylorus, and the other in the second part of the duodenum.*

Both had been filled with barium sulphate paste and some has escaped from the gastric tube.

again. If it still remains in the stomach after the second attempt, a drink of water is given, and the opening of the pylorus to allow some of this to pass, generally lets through the tube. In the first nine experiments it rarely took more than half an hour to get the tube in position in the duodenum. The actual



passage of the tube through the pylorus was not noticed by any subject.

X-rays showed clearly the position of the tube in the duodenum. In Fig. 3 it is in the position where it was usually seen in the second part of the duodenum. In one plate which was taken the tube had not turned downwards, so it must have been in the first part of the duodenum. This result did not differ from the others.

Fig. 4 is a photograph of the apparatus which was used.

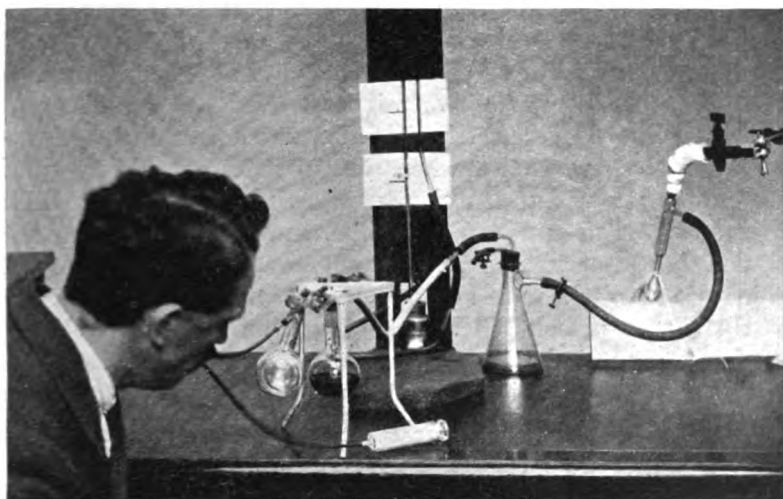


FIG. 4.

*Photo of the apparatus in use.*

The gastric tube is connected with a syringe, and the duodenal tube with the suction pump. The duodenal contents can be diverted to either flask by a three-way tap. A manometer records the negative pressure and the large flask prevents reflux of water when the suction is diminished.

The gastric tube is connected with a syringe which lies on the table ready for a specimen to be drawn off. The duodenal tube is fitted to a three-way tap, with as small a dead space as possible, leading to two small flasks. These are fitted with rubber corks, and two holes are bored for a delivery tube leading to near the bottom and for a suction tube from near the top of the flask. In the photograph, duodenal contents are seen in one of the flasks. The suction tubes from the two flasks lead to a second three-way tap, connected with the water-pump, so that a negative pressure can be produced inside the duodenum. By switching over the three-way taps and by changing the flask not in use, continuous samples can be collected from the duodenum.

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The large flask is inserted to prevent fluid coming back, when the negative pressure is diminished. A manometer is also in position so that the negative pressure may be measured. In most experiments a negative pressure of about 300 mm. Hg was used, but probably less than this would be found almost if not quite as suitable.

After most of the experiments described in this paper had been made, our attention was drawn to a recent paper by Lim, Matheson and Schlapp.<sup>7</sup> They have devised an almost identical technique, but were applying it to a rather different problem, namely the response of the stomach to histamine.

When drinking water and acid, the rate of emptying and the changes in acidity are so rapid that it is best to take samples from the stomach every five minutes. The duodenal samples are also collected separately for each five minutes by turning over the three-way tap when the gastric sample is taken. Sometimes if any sudden change takes place, *i. e.* the sudden appearance or disappearance of bile, samples are collected for a much shorter period. In this way some specimens are obtained which are almost a pure mixture of bile and pancreatic juice.

Up to the present there has only been time for a limited number of experiments, so that the following conclusions must be regarded as provisional. Perhaps an idea of the course of events is best obtained by describing a single experiment.

### DETAILS OF A SINGLE EXPERIMENT

#### *Expt. 5.—Subject, F.J.M. April 12, 1923.*

Both tubes were swallowed easily in a practised subject at 9.30 a.m. After about five minutes walking about and a quarter of an hour lying on the right side, the subject was examined with x-rays and the longer tube was found to be in the duodenum. On returning to the laboratory this was confirmed by finding that, after drinking 100 c.c. of water, nothing could be sucked up the duodenal tube, and that 155 c.c. (the water which had just been drunk and the resting juice which had not been drawn off) could be sucked up the gastric tube.

At 10.0 an ordinary gruel meal of 500 c.c., containing no salt but a measured amount of sodium phosphate, was drunk. This was added so that by estimating the phosphate in aliquot portions of each specimen recovered, it could be seen whether all the meal had been sucked up through the duodenal tube, and if not how much had passed on into the intestine. The phosphate interferes with the titration of free acid and makes

this unreliable, but previous experiments had shown that it did not influence the test-meal result in other ways.

Gastric specimens were withdrawn each quarter of an hour until the stomach seemed practically empty. Duodenal specimens were withdrawn by continuous suction all the time, and were collected in separate flasks each quarter of an hour. Each specimen, gastric and duodenal, was titrated with dimethyl and phenolphthalein, and its chloride content was estimated by Volhard's method.

The results are given fully in Appendix I at the end.

In all 623 c.c. were recovered, and as only 500 c.c. had been drunk a large proportion of the gruel and the various secretions added to it must have been recovered. The meal contained 0.36 per cent. phosphate or 1.8 grms. (estimated as  $P_2O_5$  with uranium acetate). One-quarter of each sample withdrawn was set aside for estimation of phosphates. Assuming that these samples were representative of the whole, 1.6 grms. of  $P_2O_5$  were recovered. If none was added in bile and other secretions eight-ninths of the whole meal was recovered, and one-ninth passed on down the duodenum. This amount of phosphate would be dissolved in 77 c.c., so that the original meal of 500 c.c. was increased in bulk to 700 c.c. by the various secretions which were added. This is a minimal figure which would be increased if the amount of phosphate in the bile could be taken into account.

As no chloride was taken with the meal the amount recovered must have been added by the various secretions. In all 1.05 grms. were recovered, and as the same proportion was probably lost in the duodenum 1.2 gm. must have been added. If 200 c.c. is all that was added this would represent a percentage of 0.6 for the mixed gastric and pancreatic juices and bile. There are many difficulties in this side of the investigation. It should be possible by finding some substance which can be estimated readily, is not absorbed in the stomach, does not affect the result of the test meal, and is not present naturally in any of the secretion of the upper alimentary tract, to get reliable information about the amount of digestive juices added to different types of meal. We are continuing work along these lines.

#### RESULT OF SIMULTANEOUS GASTRIC AND DUODENAL SAMPLING

It may be objected that suction in the duodenum changes the course of gastric digestion so much, and causes the stomach contents and bile to enter the duodenum more quickly than

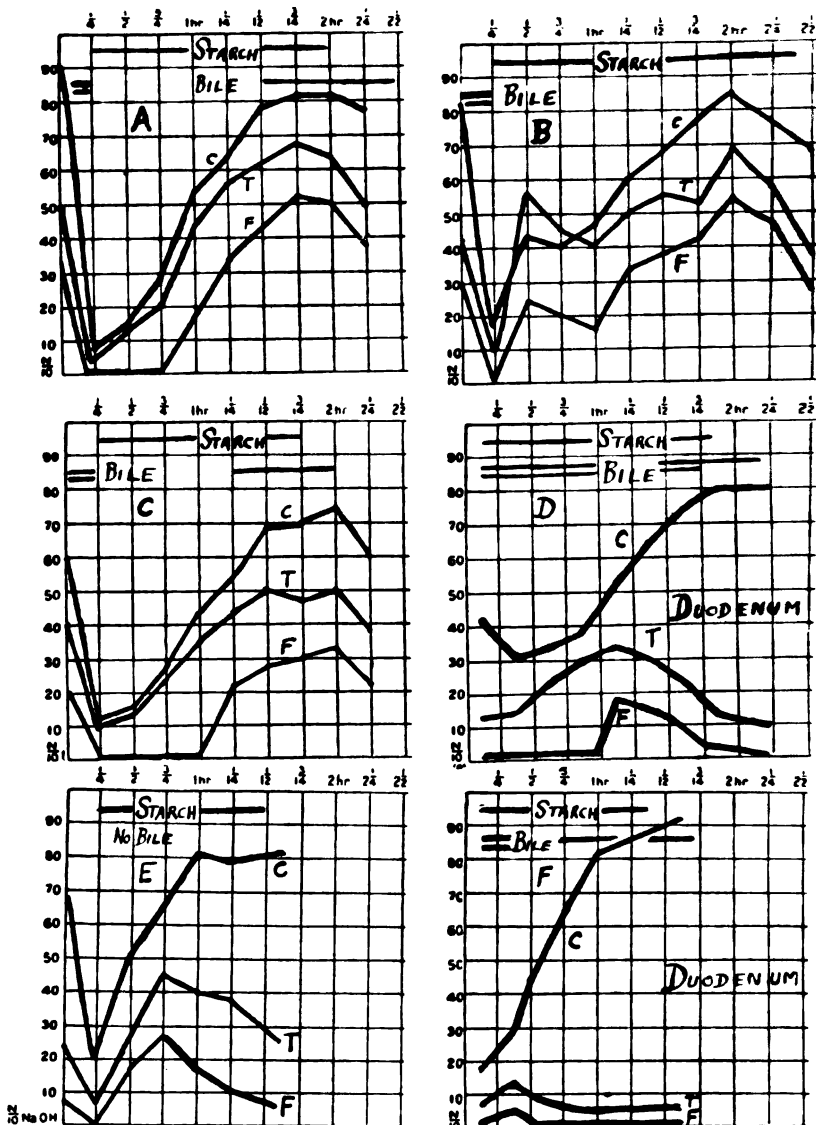


FIG. 5.

Similarity of test-meal curves under various conditions (A, B and C); and simultaneous gastric and duodenal curves (C and D; E and F; see text).

Upper line C, chloride; middle line T, total acid; lower line F, free acid.

A. F.J.M., March 1923; 500 c.c. gruel and 20 minutes later 200 c.c. lemonade with bicarbonate. (A gruel meal in the ordinary routine six months before had given a very similar curve.)

B. F.J.M., March 1923; 500 c.c. gruel and 20 minutes later 200 c.c. lemonade with 5 c.c. HCl dil. (The total acid is higher than the chloride because of the citric acid in the lemonade.)

C. F.J.M., April 1923; 500 c.c. gruel with 8 grams  $\text{Na}_2\text{HPO}_4$ , with a second tube in the duodenum through which continuous suction was applied.

D. Duodenal curve at same time as C. (C and D are Expt. 5 in text and Appendix.) If nothing was added in the duodenum the percentages in the duodenal curve should lie between the two corresponding values on the gastric curve, as the former specimens were collected continuously each fifteen minutes, and the stomach contents sampled at the beginning and end of this period.

E. M.B., March 1923; gastric curve after 500 c.c. gruel. (Cf. Fig. 2B.)

F. Duodenal curve at same time as E. Most rapid emptying appeared to be between 20 and 25 minutes. 65 c.c. were recovered, and this must be a minimal figure.

normally, so that no reliable picture can be obtained. Our experiments show that this is certainly not true. The test meal is the same whether the duodenal tube is employed or not, and as the subject feels perfectly comfortable throughout it is reasonable to assume that a fairly normal result is obtained.

In Fig. 5, A and B show the effect of adding acid and alkali. In one, twenty minutes after the ordinary gruel meal, the subject drank 200 c.c. lemonade containing 5 c.c. acid. hydrochlor. dil. (B.P.). The acid at once rose, and the effect of the citric acid which was also present was seen by the acidity being above the chloride. But the early increase of acidity seemed to lead to the production of less acid and the final part of the curve and the rate of emptying was just the same. In the other, 200 c.c. of lemonade containing 2 grms. each of sodium bicarbonate and bismuth carbonate was drunk twenty minutes after the ordinary gruel meal. Again, except for the initial lowering of acidity, the effect is not very great. A small amount of bile regurgitated into the stomach which emptied a quarter of an hour earlier, but no stress can be laid on this.

C shows the gastric curve on F.J.M. after a gruel meal, when continuous suction was applied to a duodenal tube, throughout the meal. The details are given in the appendix, and here it is only necessary to point out that the curve is not much changed. An ordinary routine test meal six months previously, when chlorides were not estimated, had given almost exactly the same result as A. Under these very varied conditions, where they might be expected to differ, the test meal curves are closely similar. Bile is always present in the resting juice, and returns later during the meal in three of the four specimens. The total chlorides rise to 0.25 per cent. or just above between 1½ and 2 hours, and then fall slightly; and the total acid is always 0.18 or slightly above during the same period.

The same thing is shown in M.B. There is little difference between his test-meal curve with and without the duodenal tube and suction (cf. Figs. 2B and 5E). It is true that in his case the stomach empties half an hour sooner when suction is applied to the duodenum, but it is doubtful if this is a significant difference. It is clear that the tube in the pyloric canal and the negative pressure in the duodenum do not change the conditions so much that conclusions about the normal course of events are of doubtful validity.

As Fig. 5 is the first one showing the curves from the duodenum, a few words of explanation may be added here. In each case the same three examinations of the contents of the

duodenum were made—the free acid (which was generally absent), the total acid, and the chloride contents. Generally the duodenal specimens were collected for five or fifteen minutes and the gastric specimens at the beginning and end of this period. Consequently, if much change was taking place in the stomach exact agreement cannot be expected, but the duodenal contents will be somewhere between the two values obtained from the gastric contents. It is further complicated by the addition of bile and pancreatic juice. The acidity of the gastric contents will be more or less completely neutralised by these—especially by the bicarbonate of the pancreatic juice. This is shown in Fig. 5—completely in F—partially in D, where more acid was coming from the stomach.

It is not known accurately what percentage of chloride is contained in human bile or pancreatic juice under normal conditions. Most of the figures given are for dogs and practically all are from juices collected through a fistula. For reasons which will be given later we think that the bile (perhaps mixed with pancreatic juice) in as pure a form as we have obtained it contains about 0.2 per cent. chloride. If this is added in small amounts to gastric contents it will not affect the chloride percentage very much, and may raise or lower it, though we have no definite evidence of the latter occurring. If it is added in larger amounts it may raise the total chloride considerably, especially where there is little chloride in the stomach. These theoretical points are borne out by the results; as a rule there was close agreement between the chloride percentage of the gastric and duodenal specimens.

With the acid it was quite different. Generally the gastric HCl was at once neutralised. In most specimens free acid did not occur, and total acid was low. It was only when the acid in the stomach was high and the emptying rapid that neutralisation was not complete.

The unexpected result is that in the stomach the curves for chloride and for acid remain as widely separated as in the earlier test meals (cf. especially Figs. 2B and 5E and 5A, B and C). It may be objected that the suction does not prevent duodenal regurgitation, and traces of bile were present in the stomach in 5C during the latter part of the meal, as they had been on one occasion previously. Certainly most of the bile is prevented from coming into the stomach, for the duodenal contents are nearly always deeply bile-stained, and it is only occasionally that the least trace of bile is present in the stomach. Still, this particular experiment is not quite conclusive, because there is some regurgitation of bile.

With M.B. it is quite conclusive. Bile is never present in the stomach (Figs. 2A, 2B and 5E). There is particularly wide divergence between his chloride and acid curves both times. It seemed possible, but not likely, that in his case pancreatic juice was able to regurgitate without bile because no bile was present in the duodenum. Examination of the duodenal specimens showed that they were all strongly bile-stained. Suction was therefore completely effective in preventing the regurgitation of bile, and it is certain that it was equally effective in preventing the regurgitation of pancreatic juice.

To explain this difficulty of the apparent regurgitation of alkali without bile, it seemed possible though rather unlikely that pancreatic juice regurgitated at a time when bile was not being excreted. These experiments exclude that explanation. What other possible sources of alkali remain? As far as possible saliva was not swallowed, and in any case it is almost neutral in reaction. Bennett and Ryle mention the secretion of the pyloric mucus as a possible source of alkali, but lay more stress on the dilution by mucus than on actual neutralisation by alkali.

In most modern works on digestion little or nothing is said about any special function of the pyloric cells, but Schafer quotes various experiments showing that the pyloric secretion is distinctly alkaline if separated from the rest of the stomach.<sup>6</sup>

It seems clear from these experiments that it is often the pyloric part of the stomach which neutralises the acid of the gastric juice and that regurgitation of pancreatic juice is not necessary. Possibly there are other cases when regurgitation of pancreatic juice is the main factor in producing neutralisation.

A few points, about which the results obtained with the duodenal tube are of interest, will be discussed shortly.

#### THE REACTION OF THE DUODENAL CONTENTS

Generally the gastric HCl is neutralised as soon as it passes the pylorus, presumably by the addition of pancreatic juice. 5F shows this well for a gruel meal and 6A for water. Under most conditions the titrations are remarkably constant, showing no free acid with dimethyl and less than 0.03 per cent. total acid with phenolphthalein. At times the reaction is considerably more acid than this. Examples have already been given of weak acid of the duodenal contents after gruel, but 6D after drinking acid, shows the presence of strong acid in the duodenum (see later). In no case was free acid found in the duodenum after water, even in those subjects in whom water provoked a con-

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siderable gastric secretion (Fig. 6A). Like previous observers,<sup>8,9</sup> we have found that some subjects give a copious secretion of acid with water and some do not.

Generally after gruel the duodenal contents are acid to dimethyl at some stage, most commonly after about an hour when the gastric HCl has risen, and the mechanism of neutralisation is perhaps partially exhausted. Naturally the most acid duodenal contents have been found after drinking acid. Once when N/10HCl was drunk the early specimens were almost completely neutralised, but after 20 minutes the acid of the stomach had been reduced to about N/20, the mechanism of neutralisation seemed to be completely exhausted and N/20 acid was recovered from the duodenum in large amounts.

In several experiments duodenal contents which appeared to be a fairly pure mixture of bile and pancreatic juice have been obtained. Sometimes this was judged by absence of gruel—other specimens being obviously cloudy; and sometimes by sudden changes in titration of duodenal specimens without corresponding gastric changes. These specimens generally gave no free acid, low total acid (about 0.05), and chloride between 0.15 and 0.25 per cent. They were a deep golden yellow colour and were probably the nearest approach to pure bile which we have found. No tests have been done to see how far they are mixed with pancreatic juice.

### THE OPENING OF THE PYLORUS

The picture of the rate of emptying is most striking. Very soon after the meal has been taken fluid arrives up the duodenal tube in gushes, reminding one of the appearance with x-rays after a barium meal. Bile appears very quickly, in most cases in the first minute, but sometimes a large amount of fluid passes into the duodenum, before any bile can be seen. The early appearance of bile confirms the view that its secretion in the early stages of digestion is under nervous control. It hardly seems possible that any chemical mechanism could be effective in forty seconds. The appearance of the bile is not due to the suction through the duodenal tube, for in many subjects this was applied before the meal, and nothing could be obtained until the meal was taken. If water was injected down the duodenal tube, it could sometimes be recovered at once unchanged, but frequently it provoked a flow of bile. Ivy<sup>8</sup> has described appearances almost exactly the same as these in dogs with a duodenal fistula.



In discussing the relaxation of the pyloric sphincter and the factors controlling this, two stages must be distinguished. On examining the stomach with x-rays after an opaque meal or by this method, it can be seen that almost at once as each peristaltic wave reaches the pylorus, the sphincter relaxes sufficiently to allow some of the gastric contents to be forced through into the duodenum. It is well known that the activity of this process just after the meal has been taken is no guide to the time at which the stomach will be found to be empty. Frequently when peristalsis is slight or absent the stomach will empty extremely rapidly, *e. g.* in cases of achlorhydria. Frequently when peristalsis is very vigorous the stomach will contain a large amount of food after four or even six hours.

Presumably for emptying to take place rapidly, or for regurgitation from the duodenum to the stomach to occur, more complete relaxation of the pylorus is needed. This does appear to be associated in some way with the degree of acidity of the gastric contents. In this connection it is interesting to record the unpublished observation of Mr. T. W. Turner, that in patients with achlorhydria he finds the tube reaches the duodenum within a few minutes, while in patients with hyperchlorhydria, it is more difficult or sometimes impossible to get the tube into the duodenum. In the latter case, it may be that the failure of the sphincter to relax is rather the cause of the hyperchlorhydria than the effect.

The rate at which fluid could be recovered through the duodenal tube, *i. e.* the degree of relaxation of the pyloric sphincter, was very variable. In Expt. 2, where R.J. drank 300 c.c. of water, 100 c.c. were recovered through the duodenal tube in the first four minutes without any bile; during these four minutes the flow was almost continuous, and then the flow came in characteristic squirts at about two minutes interval. During the next eight minutes 54 c.c. were obtained in squirts, and bile only appeared at the end of this time, *i. e.* at the twelfth minute.

A different result was obtained in R.J. with acid lemonade (Expt. 3). In the first minute 3 c.c. were obtained which were bile-stained. In the next two minutes 19 c.c. appeared in squirts strongly bile-stained. Nothing appeared in the 4th and 5th minutes, and the 6th and 7th were very like the 2nd and 3rd, 28 c.c. being obtained. At this stage the pylorus must have opened widely, for 90 c.c. appeared in one minute and 66 c.c. in the next minute. Probably this nearly emptied the stomach for nothing happened during the next five minutes. In the following three minutes a further 24 c.c. were sucked up the

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duodenal tube, after which nothing further could be obtained from the stomach.

With the gruel meal the whole process is slower. For example in F.J.M., when 500 c.c. of this was taken, bile appeared almost at once and was present throughout. The great bulk of the meal left the stomach between  $\frac{1}{2}$  hour and  $1\frac{1}{2}$  hours, and the most rapid rate of emptying was in the fifth  $\frac{1}{2}$  hour (see Appendix, Expt. 5).

Our experiments are not yet sufficiently extensive to generalise about the rate of emptying after different meals. Some of the cases where a large proportion of the meal seemed to be recovered through the duodenal tube are given in the appendix. It will be seen that with one exception (Expt. 15), after drinking water, the greater part of this passed on to the duodenum in the first five or at any rate in the first ten minutes. This seemed to be equally true whether or not the subject secreted acid after drinking water. As far as our experiments go, they suggest that some subjects consistently secrete acid into the stomach after drinking water and that others do not, and it may be that under the experimental conditions in the morning without breakfast some men are glad of a drink even of water and others do not appreciate it. With the exception of the first experiment (Fig. 5, E and F), which was done in the afternoon without lunch but after an ordinary breakfast, all were done in the morning, and the subject had had nothing to eat or drink since the evening before.

In each case where acid was given with the water the time at which most of the fluid left the stomach was later (cf. Expts. 2 and 3, 9 and 10, 12 and 18). This is rather against the view that acid on the gastric side of the pylorus has much to do with the relaxation of the pyloric sphincter.

With the gruel meal there was a greater tendency for the duodenal tube to get blocked. Except one occasion, when as much was recovered in the first as in the third  $\frac{1}{2}$  hour, the maximum rate of recovery, and therefore of emptying of the stomach, was in the third, fourth, or fifth  $\frac{1}{2}$  hour (*e.g.* Expt. 5).

### THE SUPPOSED ACID CONTROL OF THE PYLORUS.

Ordinary x-ray experience on the rate of emptying in cases with absent or unusually high acid is difficult to reconcile with the orthodox views about the acid control of the pylorus. Recently Egan<sup>5</sup>, on x-ray and experimental evidence, concluded that the usual view is unsatisfactory.

To test this further, experiments were carried out with the duodenal tube, after giving acid and alkali. Two cases will be described in detail. In J.M.H.C. 250 c.c. of water were drunk.

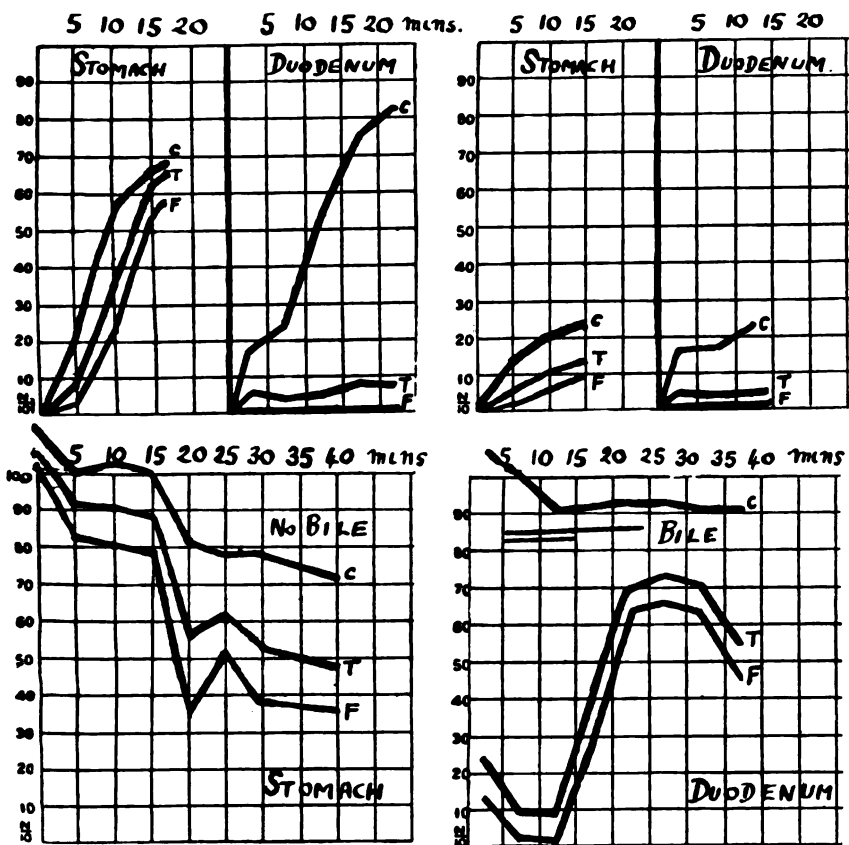


FIG. 6.

*Gastric and duodenal curves after water and acid.*

Upper curve C, chloride; middle curve T, total acid; lower curve F, free acid.

A. Stomach and duodenum after 250 c.c. water, showing considerable secretion of acid in the stomach, with neutralisation in the duodenum, the chlorides remaining practically the same (Expt. 9).

B. Stomach and duodenum after 250 c.c. water, showing little secretion (Expt. 12).

C and D. Stomach and duodenum after 200 c.c.  $\frac{N}{10}$  HCl. (See text.) (Expt. 10 in Appendix).

In all the gastric and duodenal specimens 187 c.c. were recovered. Some fluid was certainly lost by passing along the duodenum, but enough was recovered to give a good idea of the course of events. A considerable secretion of acid took place into the stomach (see Fig. 6A), but this was completely neutralised in

the duodenum. Fluid was sucked up the duodenal tube about 15 seconds after the water was finished, and during the first 10 minutes it came regularly in gushes each minute or 40 seconds. 139 c.c. were recovered during the first 10 minutes, and probably much more than this had passed the pylorus, for at 10 minutes only 6 c.c. could be obtained from the stomach. The secretion of gastric juice continued, for 4 c.c. were obtained from the stomach at 15 minutes and the same amount at 20 minutes. During these 10 minutes only 14 c.c. came through the duodenal tube. After 25 minutes the stomach and duodenum were found to be empty (Expt. 9, Appendix). In this subject 250 c.c. of water practically disappeared from the stomach in 10 minutes.

After a rest 200 c.c. of N/10HCl were drunk. 307 c.c. were recovered. Salivation was so copious that some was swallowed, but a considerable amount was spat out. Most of the increase must have been due to gastric and other secretions. Probably even more than this was secreted, for the HCl drunk contained 0.7 grm. chloride and only 0.55 grm. chloride was recovered. The 200 c.c. swallowed must have been increased to nearly 400 c.c. This calculation neglects the amount of chloride in the various secretions, which would make the figures still higher (Expt. 10, Appendix).

Figs. 6C and D show the course of events. The most striking change is that which takes place in both the gastric and duodenal samples between the 15th and 20th minutes. Before this there is little change in the stomach. The chlorides were practically the same in the gastric and duodenal contents. Although 70 c.c. of nearly N/10 acid passed through the pylorus the bile and pancreatic juice were capable of neutralising this completely. Between 15 and 20 minutes the chloride and the acidity of the gastric contents fell. This was partly due to neutralisation, but partly an actual dilution, for the chlorides fell as well as the acid, though not as much. The amount of dilution must have been considerable, for the stomach probably contained at that time between 100 and 150 c.c. It is almost certain that it was not due to duodenal regurgitation, for the suction apparatus was working efficiently, and though there was a large amount of bile in the duodenum there was no trace of bile in the stomach. The conclusion is unavoidable that under certain conditions the stomach is able to secrete a neutral or weakly alkaline fluid.

At the same time the process of neutralisation in the duodenum failed, and the contents became acid (about N/20HCl) and remained so throughout the experiment. The drop in the gastric acidity was followed by the most rapid emptying,

and 67 c.c. passed the pylorus during the next 5 minutes. The amount of bile was less than in the previous specimens, and after 25 minutes no more bile was seen. The stomach was empty in 40 or 45 minutes, so that this amount of acid definitely delayed emptying.

It follows that the high acidity during the first  $\frac{1}{4}$  hour was not such an effective stimulus to opening the pylorus as the much lower acidity in the second  $\frac{1}{4}$  hour. This cannot have been simply because acid in the duodenum neutralised the effect of acid in the stomach, for the duodenal contents were no more acid than usual during the first  $\frac{1}{4}$  hour. The experiment also shows that acid in the duodenum does not necessarily close the pylorus, for the most rapid emptying took place at a time when the duodenal contents were strongly acid.

#### SENSIBILITY OF THE DUODENUM

Hurst<sup>10</sup> has shown that the stomach is not sensitive to 0.5 per cent. HCl, and other observers have shown that even 2 per cent. acid produces no sensation. The duodenum is equally insensitive to 0.2 per cent. HCl.

The only other observation of interest was the position of the referred sensation when the duodenum was suddenly distended. If 20 c.c. of air was driven down the tube it was nearly always felt somewhere on the right side below the costal margin, while similar effects produced in the stomach were referred to the epigastrium or to the left side. The position of the two tubes could easily be distinguished in this way.

#### ACHLORHYDRIA

There are three possible causes of achlorhydria and sub-acidity—normal secretion and excessive neutralisation, diminished secretion and some neutralisation, and absence of secretion or true achylia. Bolton and Goodhart<sup>3</sup> have shown that the second is the common type in cancer of the stomach, the chloride curve being frequently at about 0.1 per cent., though often very much higher; and that the third is generally found in Addison's anæmia, the chloride curve never or rarely exceeding 0.05 per cent., apart from regurgitation of bile. The first two may certainly occur in healthy subjects, but we are doubtful if the third ever occurs in subjects who can really be called normal.

Bennett and Ryle<sup>2</sup> found that in one hundred normal students four showed complete absence of free HCl at all periods, although they had no sign or symptom of past or present disease. They stated that all these cases were confirmed by

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a second examination and by alveolar  $\text{CO}_2$  determinations, and they therefore regarded achlorhydria as a normal occurrence in a certain percentage of subjects. Largely as a result of their experience it has been widely assumed that about 4 per cent. of normal men have achlorhydria.

At first we were inclined to agree with this view, because three of these sixty students showed complete absence of free HCl and very low total HCl at their first examination. In two little resting juice could be obtained, bile was absent throughout the meal, and they were emptying at or before  $1\frac{1}{2}$  hours. In the third there were 45 c.c. of strongly bile-stained resting juice, bile was present throughout the meal in larger amounts than in any other subject, and the stomach was empty in  $1\frac{1}{2}$  hours. Even without measuring the chlorides in his secretion it seemed likely that his apparent achlorhydria might be due to excessive regurgitation. Subsequent examinations of the same three students showed that two had not constant achlorhydria, and made it doubtful if any of the three had real achylia.

As achlorhydria is of some interest and importance these three subjects will be discussed in detail. The result of their x-ray examination will also be included. This was done as a routine in all the students who were examined by the test meal, and a comparison of the results will be given in a subsequent paper, but it is more convenient to describe the x-ray findings in these three subjects here.

A. had complete achlorhydria on three occasions (October and November 1922, and April 1923). His stomach was empty twice at  $1\frac{1}{2}$  hours and once at  $1\frac{1}{2}$  hours. Bile was present once in the resting juice and twice after the stomach had ceased to contain starch, but was absent in all other specimens. The total chlorides were measured in the second and third meals, and the third time a duodenal tube was passed and specimens were withdrawn through it by continuous suction. The stomach was empty at  $1\frac{1}{2}$  hours; no bile had appeared in any specimen; and the total chlorides had only reached 0.12 per cent. In the  $1\frac{1}{2}$ -hour specimen it is true that the chlorides had risen to 0.2 per cent., but this specimen contained bile and was obtained after the stomach was empty of starch by applying suction with the water-pump to the gastric tube.

Unfortunately this was one of the experiments where the duodenal tube got blocked part of the time, so that specimens were not obtained throughout. Where they were obtained, they closely resembled the gastric specimens except for the presence of bile. It seems probable that the last gastric speci-

men was simply obtained by regurgitation from the duodenum. Even omitting this, the chloride reached 0.12 per cent. in the previous specimen where no bile was present, and as has been seen this is a higher figure than was obtained in most cases of true achylia of Addison's anæmia. He was certainly achlorhydric, but perhaps towards the end of the meal secreted a little acid which was at once neutralised.

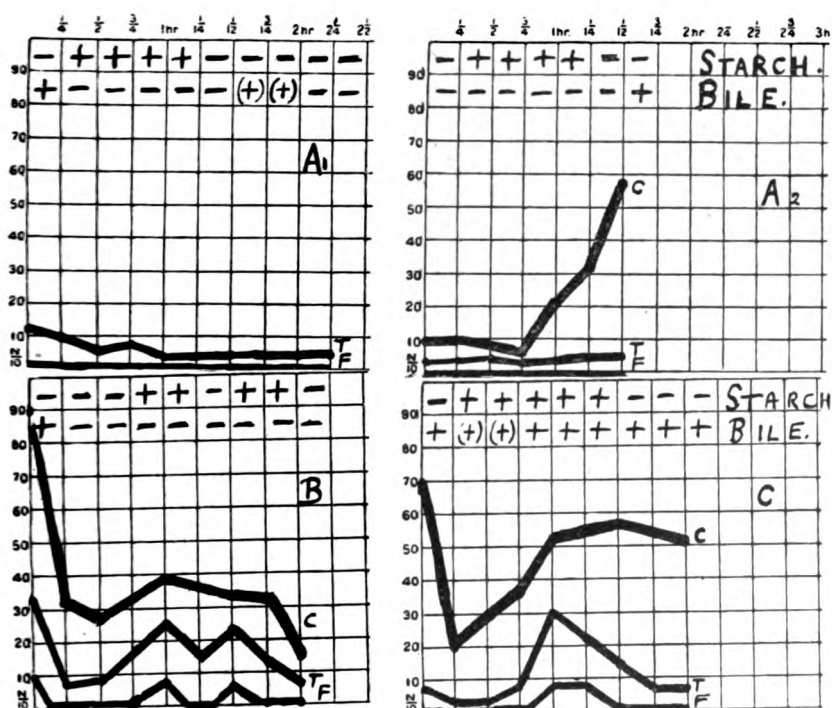


FIG. 7.

*Achlorhydria.*

Upper curve C, total choride; middle curve T, total acid; lower curve F, free acid.

A, B and C all showed achlorhydria on the occasion of their first test meal (e.g. A<sub>1</sub>). A<sub>2</sub>, B and C show the findings on later occasions when the chlorides were also estimated.

An x-ray examination at the time of his first meal showed a stomach which was normal in tone and position, but which emptied more rapidly than was usual, although no peristalsis was seen. He was a sallow individual who complained of no symptoms of indigestion, but was taking no exercise of any sort.

B. showed achlorhydria and his stomach was empty in 1 1/2 hours in October 1922. There were only 20 c.c. of resting juice and no bile was present throughout the meal. In the

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same month an x-ray examination showed that the stomach was hypotonic, low in position and slow in emptying.

Four months later the meal was repeated and the total chlorides were estimated. He had not achlorhydria. The result is given in Fig. 7B. The differences between the specimens at 1 and  $1\frac{1}{2}$  hours and at  $\frac{1}{4}$ ,  $\frac{1}{2}$ ,  $\frac{3}{4}$  and  $1\frac{1}{4}$  hours are evidence that there was not complete mixing, and that there was an upper layer with mucus (perhaps swallowed) and a lower layer with a small amount of free acid. These may suggest that representative gastric specimens were not obtained at any time; but specimens could be easily withdrawn up to  $1\frac{1}{2}$  hours. After that, even by moving the tube about, only 10 c.c. could be obtained at  $1\frac{3}{4}$  hours and 5 c.c. at 2 hours, so it seems reasonable to assume that the stomach was practically empty at  $1\frac{3}{4}$  hours and that very little acid was excreted at any time. There was certainly no excessive neutralisation, for except in the resting juice, when a considerable amount of bile was present, the total chlorides never rose above 0.14 per cent.

B. was a tall healthy-looking individual who had never complained of any gastric trouble. The only abnormality was that he had hay fever of several years standing, and gave a positive ophthalmic reaction with pollantin. He was not taking any vigorous exercise, but walked moderate distances and seemed fairly fit.

C. showed complete achlorhydria in November 1922. The specimens were strongly bile-stained throughout, and the stomach was empty in  $1\frac{3}{4}$  hours. The curve for the total chlorides did not reach 0.2 per cent. This showed that the achlorhydria was not due to excessive neutralisation of a normal amount of HCl, in spite of the presence of a large amount of bile, but it was not low enough to decide if a small amount of acid was secreted and neutralised, or if no acid was secreted.

A second test meal four months later gave the same result, except that a small amount of free acid was present in the 1 hour and  $1\frac{1}{4}$  hours specimens. This showed that the second alternative was the right one. An x-ray examination at the same time as his first test meal showed that the stomach was slow in emptying and that peristalsis was sluggish. It was classed as normal in position, but a note was made at the time that a contraction of the abdominal muscles raised it about two inches. C. was small and very sallow looking; he did not complain of any symptoms of indigestion, but during these six months he had woken up three times at night and vomited without apparent cause.



These results can be summarised by saying that B. and C. had achlorhydria once, but not when the meal was repeated. Examination of the chloride curve showed that they had extreme hypochlorhydria. A. was the only subject in a series of sixty students who showed achlorhydria each time he was examined (three times). The chloride curve was lower in his case than in any of the others, and for the first three-quarters of an hour, during which time his stomach was emptying rapidly, there was no evidence that any juice was secreted. But at 1 hour and at 1½ hours a little gastric juice, without any free acid, may have been present, so that it is doubtful if he had complete achylia. He certainly had, and was the only subject in this series who had, complete and constant achlorhydria.

The question remains—Were these three subjects, and more particularly A., in normal health? The results of the x-ray examination have been given, and it is interesting that all three were among the comparatively small proportion who showed some deviation from the normal. In A. and C. it did not seem a very big deviation, but B. was noticeably different from the average in all the three points considered. It may be urged that the x-ray findings were abnormal, because of the lack of acid. Here we only wish to emphasise that they differed from what was usual in both particulars. The x-ray examination, and the report on it, was made by Mr. J. J. Conybeare, who knew nothing about the men or about the result of their test meal. I wish to thank him for allowing me to refer to these three results here.

These three, among various others, were subjected to some tests for physical fitness. B. and C. passed in all four tests as of average fitness, but with A. the result was very different. His pulse rate at rest was 90 on three separate occasions; after exercise its rate of return was unusually slow, and his weight was more than 10 per cent. below Dreyer's standard. Outside opinion was in moderate agreement with these tests, for B. was classed as of average fitness and A. and C. as below the average. B. was in the habit of walking long distances, but A. and C. were taking no regular exercise of any sort.

The question of what is normal resolves itself largely into a verbal discussion, but it is clear that the only possible case of achylia in this series of sixty students differed from what was usual in so many respects that he can hardly be called normal, although there was no definite evidence of disease. Of the two students with extreme hypochlorhydria who showed achlorhydria on one occasion only, one appeared in normal health and the other did not.

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Obviously the absence of a case of achylia in an absolutely healthy student in this series is not sufficient evidence to decide if achylia may occur as a normal physiological variation. Apart from the theoretical interest the question is of considerable practical importance, because of the view warmly advocated by Hurst that achlorhydria is the necessary antecedent of Addison's anæmia, and that the achlorhydria is generally, though not always, due to congenital achylia.

On general principles it is unlikely that an important function such as the secretion of gastric juice will be absent at birth except as an exceedingly rare abnormality. And at present there is not sufficient evidence to show that this occurs at all frequently. Recently Chievitz<sup>11</sup> has examined 53 infants with a sweet barley-water test meal and has found no case of achlorhydria. The finding of achlorhydria or even achylia in the relatives of patients with Addison's anæmia can be explained in other ways, for a tendency to develop achlorhydria under certain conditions is quite as likely to be inherited as a congenital achylia. The subject is too long to be further discussed here.

### CONCLUSIONS

1. The curve of total chlorides during a fractional test meal gives additional information about the course of gastric digestion. It is the best measure of the amount of gastric juice secreted. The variations of this curve in twenty-six healthy students are described. The curves of total and free acidity are also useful, because they give information about the function of the gastric juice from the point of view of digestion and antisepsis.

2. Diminished secretion can be distinguished from normal secretion and excessive neutralisation by this method, while if the acid alone is determined these two are grouped together. The validity of a simple direct method of estimating chlorides is established. Probably it would prove of value in the routine investigation of dyspepsia.

3. A method is described by which samples can be obtained from the stomach and from the duodenum at the same time. This gives a good picture of the passage of food through the pylorus and of the flow of bile under almost normal conditions. Generally after water or gruel, bile appears in the duodenum within the first minute, presumably by reflex stimulation of the gall-bladder.

4. Under normal conditions the chloride curve continues to rise after the acid curve is falling or has become level. This must be due to neutralisation by alkali. The pyloric part of the stomach plays an important part in this neutralisation. In several subjects examined it was the main factor, but no doubt there are others in whom duodenal regurgitation is more important.

5. Usually the acidity of the gastric contents is neutralised on reaching the duodenum, and their reaction becomes alkaline to litmus and dimethyl, but remains acid to phenolphthalein. Under certain conditions N/20HCl may be recovered from the duodenum. This may occur when the pylorus is widely open and large quantities of fluid are passing through it. Probably the degree of relaxation of the pyloric sphincter is under reflex control, and acid in the gastric or duodenal side is only one factor influencing the reflex and may easily be overridden.

6. In the two cases examined N/20 acid produced no sensation in the duodenum. Distention of the duodenum with air or water was always referred to the right side.

7. Of sixty students examined only one showed consistent achlorhydria. There were many reasons for not regarding him as absolutely normal, and it is doubtful if he had complete achylia. Two others had extreme hypochlorhydria and achlorhydria on one occasion. One of these two was not in perfect health.

There is evidence that achlorhydria occurs in a small proportion of men who are apparently in good health, but none of these have been investigated sufficiently or watched for a long enough period to establish achlorhydria as a normal physiological variation. This applies even more to reported cases of achylia.

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## APPENDIX I

### DETAILS OF EXPERIMENTS REFERRED TO IN TEXT

Duodenum.						Stomach.					
Time.	Free acid. §	Total acid. §	Total chlor-ide. §	Quan- tity obtained (c.c.).	Pre- sence of bile.	Time.	Free acid.	Total acid.	Total chlor-ide.	Quan- tity with- drawn by syringe.	Pre- sence of bile.
Expt. 2.—Subject, R. J. March 12th. 250 c.c. water at 10.0.											
10.1—10.5	0§	2§	14§	100†	trace	10-5	0	4	22	10	—
10.5—10.13	0	2	32	54	(+)						
10.13—10.16	0	10	64	18	++						
10.16—10.20	0	6	72	55	+						
10.20—10.30	0	4	74	23	+	10-20	Stomach empty				
Total (grms. or c.c.)			0.36	250					0.01	10	
Expt. 3.—Subject, R. J. March 12th. 205 c.c. acid lemonade at 11.0.*											
11.0—11.5	24	48	80	22	++	11.5	52	124	46	15	—
11.5—11.7	36	100	56	28	++						
11.7—11.9	46	126	46	156†	+						
11.9—11.14	46	125	52	0		11.10	34	90	53	15	—
11.14—11.17	36	70	84	24	(+)						
11.17—11.20	36	74	108	10	(+)	11.15	44	80	76	5	—
Total (grms. or c.c.)			0.50*	240					0.07	35	
Expt. 4.—Subject, R. J. March 12th. 200 c.c. lemonade and carbonate at 12.0.											
12.0—12.2	0§	8§	46§	17	+	12-5	2§	20§	37§	22	—
12.2—12.5	0	6	34	44†	(+)						
12.5—12.7	2	6	24	34†	(+)						
12.7—12.13	2	8	48	26	(+)	12.10	35	54	80	10	—
12.13—12.25	10	24	90	19		12-17	58	68	96	12	—
						12-25	44	56	76	28	—
Total (c.c.)			—	140						72	
Expt. 5.—Subject, F. J. M. April 12th. 500 c.c. gruel at 10.0.											
10.0—10.15	0	12	42	27	+	10.15	0	10	12	20	—
10.15—10.30	0	16	32	86	+	10.30	0	14	14	25	—
(10.30—10.35)	(0)	(14)	(46)	(12)	? pure bile						
10.30—10.45	0	22	36	56	+	10.45	0	26	26	15	—
10.45—11.0	0	30	36	61	+	11-0	0	36	42	15	—
11.0—11.15	16	36	52	134†	+	11.15	22	44	54	15	((+))
11.15—11.30	10	30	66	25	+	11.30	26	50	68	15	((+))
11.30—11.45	4	24	74	32	+	11.45	28	48	68	17	((+))
11.45—12.0	0	14	80	25	(+)	12-0	34	50	74	15	—
12.0—12.15	0	12	80	14	(+)	12.15	22	36	60	26	—
Total (grms. or c.c.)			0.80	460					0.25	163	
Expt. 9.—Subject, J. M. H. C. Aug. 16th. 250 c.c. water at 9.0.											
9.0—9.5	0	4	20	68†	+	9.5	2	5	20	14	—
9.5—9.10	0	2	20	71†	+	9.10	26	36	54	6	—
9.10—9.15	0	4	55	7	+	9.15	54	66	66	4	—
9.15—9.20	0	6	76	7	+	9.20				4	—
9.20—9.25	0	6	84	6	+	9.25					
Total (grms. or c.c.)			0.15	159					0.04	28	

\* The chloride content of the meal in these three cases was 0.28 in Expt. 3, 0.84 in Expt. 10, and 0.49 in Expt. 13. In the other cases the meal contained no chlorides

† These acid titrations are inexact owing to presence of citric acid.

‡ Represents period of most rapid emptying.

# IN FRACTIONAL TEST MEAL SAMPLES 51

Duodenum.						Stomach.					
Time.	Free acid. §	Total acid. §	Total chlor-ide. §	Quantity recovered (c.c.).	Pre- sence of bile.	Time.	Free acid.	Total acid.	Total chlor-ide.	Quantity with- drawn by syringe.	Pre- sence of bile.
<i>Expt. 10.—Subject, J. M. H. C. Aug. 16th. 200 c.c. acid at 9.30.*</i>											
9.30—9.35	14	24	112	13	—	9.30	108	112	116	—	—
9.35—9.40	0	8	102	33	++	9.35	82	90	100	12	—
9.40—9.45	0	8	90	25	++	9.40	84	88	104	10	—
9.45—9.50	30	40	92	26	+	9.45	84	90	100	14	—
9.50—9.55	64	70	94	67†	+	9.50	34	54	74	15	—
9.55—10.0	66	74	94	16	—	9.55	56	66	78	13	—
10.0—10.5	64	70	92	12	—	10.0	36	52	78	10	—
10.5—10.10	46	56	92	32	—	10.5					—
10.10—10.15	27	37	—	5	—	10.10	36	50	72	4	—
						10.15					—
Total (grms. or c.c.).			0.79*	229					0.24	78	
<i>Expt. 12.—Subject, M. B. Aug. 21st. 250 c.c. water at 9.0</i>											
9.0—9.5	0	4	17	58†	++	9.5	0	2	10	15	—
9.5—9.10	0	2	17	7	++	9.10	4	8	20	12	—
9.10—9.15	0	2	23	6	++	9.15	7	10	22	4	—
Total (grms. or c.c.).			0.04	71					0.02	31	
<i>Expt. 13.—Subject, M. B. Aug. 21st. 250 c.c. acid lemonade at 9.30.*</i>											
9.30—9.35	0	12	66	20	++	9.35	40	44	54	14	—
9.35—9.40				0	—	9.40	42	46	54	16	—
9.40—9.45	0	5	46	49†	++	9.45	42	46	54	16	—
9.45—9.50	6	11	58	21	++	9.50	28	32		3	—
9.50—9.55	}	0	6	46	9	9.55	40	45		4	—
9.55—10.0						10.0					
10.0—10.5						10.5					
10.5—10.10	0	11	70	11	+++						—
Total (grms. or c.c.).			0.21*	110					0.10	52	
<i>Expt. 15.—Subject, H. H. Aug. 28th. 250 c.c. water at 10.30.</i>											
10.30—10.35	0	6	42	12	+	10.30	0	0	0		—
10.35—10.40	0	4	20	17	—	10.35	2	10	25	13	—
10.40—10.45	0	8	32	19	(+)	10.40	2	10	25	13	—
10.45—10.50	0	14	34	109†	(+)	10.45	2	10	28	9	—
10.50—10.55	6	16	34	9	++	10.50	0	10	32	16	—
10.55—11.0	6	16	36	16	+	10.55	0	14	30	12	—
11.0—11.15	8	18	62	15	+	11.0	0	16	40	16	—
						11.10	12	28	72	12	—
Total (grms. or c.c.).			0.22	197					0.12	91	
<i>Expt. 16.—Subject, H. H. Aug. 28th. 250 c.c. water at 11.30.</i>											
11.30—11.32	0	10	68	6	+++						
11.32—11.35	0	8	22	48†	+						
11.35—11.40	2	12	22	46†	+	11.35	4	14	24	11	—
11.40—11.45	0	6	24	6	+	11.40	6	16	22	13	—
11.45—11.50	0	8	34	15	+	11.45	6	18	28	12	—
11.50—11.55	0	10	40	16	+	11.50	6	16	30	12	trace
11.55—12.0	0	16	47	9	++	11.55	0	16	42	8	trace
Total (grms. or c.c.).			0.11	146					0.06	56	

§ All acidity figures refer to c.c. of N/10NaOH needed to neutralise 100 c.c. of gastric juice or duodenal contents. Chloride is referred to the same scale instead of being represented as percentages, to make comparison easy.

## APPENDIX II

## THE ESTIMATION OF CHLORIDES IN GASTRIC SAMPLES

In investigating the inorganic chlorides in gastric contents, it has been usual to fuse the sample before adding silver nitrate and titrating with thiocyanate as in Volhard's method. This is theoretically preferable, owing to the unknown effect of the protein and other substances present, but it has made the method so laborious that it cannot be applied easily to the fractional test-meal samples. It seemed reasonable to suppose that the total chlorides could be obtained with sufficient accuracy by a direct Volhard determination, and that if their total acidity (calculated as chloride) was deducted from this it would give a measure of the inorganic chlorides. This process can be applied fairly easily and rapidly, and it would therefore be of considerable advantage were its validity established.

To test this, mixtures were made up containing a measured amount of hydrochloric acid and of test meal (A — N chloride free; Q — Z chloride content 0.14 per cent.) and sometimes of sodium chloride, added directly or produced by neutralising some of the hydrochloric acid with sodium hydroxide. From the composition of the mixture the exact content of acid chloride, inorganic chloride and total chloride could be calculated (columns A, D and G in Table I, where all the results are given). With each mixture five determinations were made—the chloride content determined directly by Volhard's method (subsequently referred to as "total chloride") and indirectly by Volhard's method after neutralising and ashing, the inorganic chloride by Volhard's method after ashing, and the "free" and "total" acidity by the usual titrations with dimethyl and phenolphthalein.

The table shows that the total chloride can be estimated with reasonable accuracy by Volhard's method without ashing. In these seventeen determinations, nine gave a result too high with an average error of .01, and eight were too low with an average error of .012. The greatest error, which only occurred once, was .02. As the exact position of the end-point produces an error of .01, there is little other error introduced in this estimation. In these experiments the error in determining the total chloride after neutralisation and ashing was actually a little greater and twice exceeded .02. Probably this is not generally true, but we have much greater experience of the direct method, having done many hundreds of determinations in the last few months and comparatively few after neutralisa-

tion and ashing. For most clinical purposes the direct is quite as accurate as need be.

The titrations with dimethyl and phenolphthalein do not give the actual acidity, but the table shows that where the acidity is above 0.2 per cent. the "free acid" and the real acid are in very close agreement, and where the acidity is below 0.1 per cent. the real acid is given very accurately by the average of the "free acid" and the "total acid," the average error being less than 0.01.

Obviously in cases where the only acid present is hydrochloric acid the inorganic chloride can be obtained by subtracting the average of the "free" and "total acid" from the total chloride. As the error of each determination is less than .01 the error in the result cannot be greater and may be less than .02. This calculation is given in columns L and M. In 12 cases the result was too low with an average error of .012, and in 5 cases it was too high, with an average error of .008. If the inorganic chloride is obtained by subtracting the "free acid" from the total chloride the result is less sound theoretically, but it is not much worse practically, the average error being .014 (column K). The method which was first thought of, *i. e.* subtracting the "total acid" from the total chloride is much less accurate, having an average error of .023 and several times an error of .04 (5 times in 17 expts.). In the other two methods of calculating the inorganic chloride there are only 9 determinations out of 34 where the error was greater than .02, and it was never greater than .025. This method of determining the inorganic chloride (*i. e.* deducting the "free acid" or, better, the average of the "free acid" and the "total acid" from the total chloride) is not as accurate as the standard method of Volhard determination after ashing (column H), but it is sufficiently accurate for most purposes. The average error is .012, and it is never greater than .025 per cent. chloride.

TABLE I.  
CHLORIDE CONTENT AND ACIDITY OF KNOWN SOLUTIONS BY VARIOUS METHODS

Ingredients of mixture.	Total chloride.			Total acid (as chloride).			Inorganic chloride.				
	Actual amount present.	Found by Volhard (direct).	Found by Volhard after ashing.	Actual amount present.	Found by titration "Free."	Found by titration "Total."	Actual amount present.	Found by ashing.	Calculated B-E.	Calculated B-E + F/2.	Error in using the last column.
A.— 1 part N/10HCl 9 parts Test meal	.065	.075	.05	D. .03	E. .005	F. .06	G. .035	H. .03	K. .07	L. .045	M. +.01
B.— 5 parts N/10HCl 7 parts Test meal	.12	.105	.095	.09	.07	.115	.03	.035	.035	.015	-.015
C.— 5 parts N/10HCl 5 parts Test meal	.17	.17	.155	.15	.135	.175	.02	.03	.035	.015	-.005
D.— 7 parts N/10HCl 3 parts Test meal	.22	.23	.21	.21	.215	.235	.01	.025	.015	.005	-.005
E.— 9 parts N/10HCl 1 part Test meal	.275	.26	.25	.27	.27	.28	.005	.005	-.02	-.01	-.015
H.— 10 parts B, 3 parts H <sub>2</sub> O 2 parts N/10NaOH	.08	.09	.075	.02	.005	.04	.06	.045	.085	.07	+ .01
K.— 10 parts C, 3 parts H <sub>2</sub> O 2 parts N/10NaOH	.115	.12	.125	.06	.05	.08	.055	.06	.07	.055	0
L.— 10 parts C + 5 parts N/10NaOH	.115	.12	.13	0	0	.02	.115	.11	.12	.11	-.005
M.— 10 parts D + 5 parts N/10NaOH	.145	.16	.125	.04	.045	.05	.105	.105	.115	.115	+ .01
N.— 10 parts E + 5 parts N/10NaOH	.185	.18	.19	.08	.085	.09	.105	.120	.085	.085	-.01
X.— 2 parts N/10HCl 8 parts Test meal	.145	.135	—	.035	0	.06	.11	—	.135	.105	-.005
Y.— 2 parts HCl, 2 parts NaCl 6 parts Test meal	.135	.12	—	.035	.02	.06	.10	—	.10	.08	-.02
W.— 6 parts N/10HCl 4 parts Test meal	.155	.14	.15	.10	.09	.125	.055	.06	.05	.035	-.02
Z.— 6 parts HCl, 2 parts NaCl 2 parts Test meal	.14	.125	.14	.10	.10	.12	.04	.04	.025	.015	-.025
Q.— 5 parts NaCl ...	.12	.115	—	.09	.08	.085	.08	—	.035	.035	+ .005



## CHRONIC SPASM OF THE COLON

By PHILIP TURNER, M.S., Surgeon to Guy's Hospital.

For some years past I have been very interested in a number of cases in which a portion of the large intestine, usually the pelvic colon as it crosses the left iliac fossa, can be readily felt on abdominal palpation, giving, as it is rolled under the fingers, the impression that it is a hard, thick-walled, rigid structure.

The large intestine may be easily palpable and recognisable as the result of a number of different causes. It may be distended with flatus, a condition characterised by its size and the tympanitic note obtained on percussion; it may be loaded with faeces, which can be distinguished by the character of the masses felt, by the history of constipation, and by the effect of enemata and purges; it may be due to an inflammatory lesion, which can generally be recognised after consideration of the signs and symptoms and the information derived from observation and examination; it may be due to a neoplasm, which can usually be diagnosed from the history of the case, the symptoms, and the result of an x-ray examination; or it may be the result of thickening and hardening of its walls brought about by muscular contraction.

It is of this last group that I wish to speak, and which, on the assumption that it is the result of a tonic contraction of the involuntary muscle of the bowel wall, may be described as chronic spasm of the colon, or, to use a convenient abbreviation similar to those applied to spasm in other portions of the alimentary tract, Colospasm.

Cases of this kind are by no means infrequent. In many the condition is only found in the course of a routine abdominal examination, possibly where there is a lax abdominal wall. Symptoms may be entirely absent, and although the ease with which the colon can be palpated and the character of the viscus are striking, yet considerable doubt may be felt as to whether there is really any abnormality at all.

In other cases the patient complains definitely of abdominal symptoms, and it is in the course of an examination to find an explanation of these that the surgeon finds a hard, rigid colon, which is definitely tender on pressure. In such cases, especially

where after observation and investigation no other cause for the symptoms can be found, it is often impossible to avoid the conclusion that some abnormal condition of the colon is present.

The degree of hardening and the extent of colon involved varies considerably in different cases. It is most commonly felt where the large intestine crosses the left iliac fossa. This is just where one would expect the colon to be most easily palpable, for it is here in close relation with the anterior abdominal wall, and can be rolled under the fingers against the iliacus muscle which brings it well forward. As it is traced upwards the descending colon is more deeply placed, while posteriorly it is not supported by the iliac fossa, but is in relation with the muscles of the abdominal wall. It is thus palpated with much greater difficulty, and when the iliac colon can be felt as a thick rigid tube, the descending colon, though it can usually be felt to be in the same condition, becomes less and less distinct as it is traced upwards towards the splenic flexure. This may be the only part of the large intestine affected, or a similar hardening of the cæcum and the ascending colon may be felt. Some of these cases, especially where this part of the colon is alone affected, may bear a very close resemblance to sub-acute appendicitis, and possibly in some cases where this diagnosis has been made, and where, on removal, the appendix appears to be normal, the explanation may be that there has been spasm of the cæcum and ascending colon, causing pain and tenderness and simulating a tumour.

Much more rarely the transverse colon may also be felt to be in the same contracted, rigid condition. That this portion of the large intestine can be so seldom felt is probably due to the fact that it is a movable structure, and that it is situated mainly behind the rectus muscles, which prevent it from being rolled under the fingers against the posterior abdominal wall.

The hard and contracted colon is tender on pressure except in those slight cases which commonly also do not cause any symptoms, and it is not uncommon to find that in cases where a tender hard colon can be felt in the left iliac fossa, tenderness can also be elicited in the course of the transverse colon, though it may be impossible to feel the bowel and roll it under the fingers.

Though, as has already been stated, in some of the cases symptoms are absent, yet in many the condition is discovered in the course of an examination to ascertain the cause of some abdominal pain or discomfort. As a rule the patient gives a history of abdominal pain, not of great severity, but persistent with intermissions and remissions over a long period. Though

usually referred to the umbilical region, it is often variable in situation or may be described as general. It improves with rest in bed, but reappears when the patient gets about again. The pain has no relation to food; there is no vomiting, and the bowels are usually described as acting normally, or there may be a moderate degree of constipation; diarrhoea does not occur, and the motions contain neither mucus nor blood.

Many of the patients have been previously operated upon for chronic appendix trouble, and several other of my cases have been referred to surgical out-patients as cases of chronic appendicitis. In the latter the slightly tender thickened cæcum and ascending colon probably suggests this diagnosis, but palpation reveals a very similar mass on the left side. In the former it is possible that the original symptoms may have been due to colospasm, but it is also possible that a similar condition may have been present in the appendix itself, perhaps causing "appendicular colic": in some cases, too, the spasm is secondary to chronic appendicitis. The relationship of colospasm to chronic appendicitis is thus a matter of considerable clinical importance. On the one hand, colospasm should be considered in the diagnosis of some obscure cases of chronic appendicitis; on the other hand, it must be remembered in those very troublesome and not infrequent cases where the appendix has been removed and, after a certain period of relief, the patient reappears complaining of abdominal pain closely resembling that for which the operation was originally performed. There are a good many causes for the persistence of pain after appendicectomy, but in some, especially those vaguely attributed to "adhesions," often without x-ray or other positive evidence, this spasm of the large bowel will be found, and is probably then the explanation of the persistence of symptoms.

I have admitted several of these cases to hospital for observation and investigation, and have also had a number under observation and treatment at out-patients. In all these x-ray examination has failed to show any lesion or change in the large bowel; in no case has blood or mucus been present in the motions, while purges and enemata have been without effect. In this way an inflammatory condition, a neoplasm, and loading of the bowel with fæcal masses can be excluded, and one is driven to accept some form of tonic contraction or spasm of the muscular tissue of the colon as the explanation. Usually with rest in bed the pain diminishes, and in most cases rapid relief of symptoms and diminution of the spasm follows on the administration of belladonna and hyoscyamus.

Spasm of the involuntary muscles of the alimentary tract is

a well-recognised condition, which was summed up by de Bec Turtle<sup>1</sup> in his address before the Harveian Society last year. Of these cardiospasm, pylorospasm, enterospasm, and anal spasm are the best known, though the first is not a true spasm but is due to difficulty in relaxation of the cardiac sphincter (Achalasia).

Enterospasm, or more correctly acute colospasm, a form of severe spasm of a localised portion of the colon is thus described by Lockhart Mummery.<sup>2</sup> "This is the name given to a condition in which there is spasmodic contraction of the circular muscle fibres in some portion of the colon. The contraction of the colon is localised to one spot, and varies from one to several inches in length. So intense is the constriction that the bowel lumen is partly or completely closed, and symptoms of intestinal obstruction occur. The condition is comparable to asthma and spasmodic stricture of the urethra. . . . In addition to the symptoms caused by the enterospasm there are usually those of a chronic colitis. The stools contain much mucus and often blood. There is constipation alternating with periods of diarrhoea, and all the other symptoms usually associated with a chronic colitis. In the more severe cases faecal vomiting and visible peristalsis may also be present."

This is clearly a much more acute and more localised form of spasm; also it is generally accompanied by definite evidence of colitis. Colospasm differs from the spasm described by Mummery in that it is the result of some more chronic and diffuse muscular contraction, that it is more persistent, and that it is unaccompanied by the symptoms of colitis.

Hurst, in his book on *Constipation*,<sup>3</sup> considers the clinical aspects of the various spasmodic affections of the colon. He finds that chronic spasm is commonly associated with more or less severe constipation, and that there is also often spasm of the sphincter ani, so that the stools have the form of thin tape-like masses. He states that spastic constipation—that is, constipation associated with spasm of the colon—may arise from: (a) Irritants acting from within the intestine, such as hard faecal masses, ascarides, or irritating ingredients of the diet; (b) toxic causes, such as lead, tobacco, and occasionally caffeine from excessive drinking of tea or coffee; (c) reflex, secondary to chronic disease of the abdominal viscera such as gall-stones, appendicitis, duodenal ulcer, or salpingitis; (d) tabetic, intestinal crises being probably due to spasm.

Hurst also points out that chronic spasm of the colon was described as long ago as 1880 by John Howship, but that for over fifty years his description was forgotten and that it is

only in the last twenty years or so that interest has been revived in these cases of spasm.

The cause of this peculiar hardening and contraction of the colon is the subject of a paper by T. Stacey Wilson, entitled "A Physiological Explanation of Pain due to Functional Disturbance of the Muscles of the Colon."<sup>4</sup> In this paper he quotes Sherrington,<sup>5</sup> who has shown that muscular fibres in addition to the power of contraction have another form of activity, to which he applies the term "postural activity," because it plays so important a part in maintaining the posture of the body. The subject is too long and too complex to discuss here, but I may quote the following summary of Sherrington's conclusions from Stacey Wilson's paper :

"In their postural or tonic activity the tension of muscles or muscle fibres is largely independent of their length. Therefore a ring-muscle, for example, in the gut, may quite well assume a 'cartilaginous' hardness and yet maintain a ring-shape of any desired lumen—or if requisite might presumably obliterate the lumen. The case of the gut is quite analogous to the bladder or stomach; the musculature of these latter will exert no more pressure upon 200 c.cm. than on 50 c.cm. They grasp their content with the same pressure independently of the length of the muscular fibres, just as the hand can grasp an orange with the same light pressure as a walnut."

"He also uses the following simile :

"Perhaps I can put the notion briefly by comparing the muscle fibre to a plaster of Paris brick, which would set and unset at the direction of a nerve. If a six-inch brick were desired it flowed into a six-inch length and there set; if a three-inch, then it must unset from the six-inch length, become three inches shorter and proportionately wider, and set again. If a nine-inch brick, conversely."

"In these observations of Prof. Sherrington we have a perfectly satisfactory explanation of the hardening of the colon with which we are clinically familiar. We may not yet be quite certain as to the relationship between the postural activities of the colon muscles and their contractile functions, but this point is, I think, immaterial to the present argument. In the normal bowel there must be perfect co-ordination of these two types of muscular activity, otherwise a conflict between them would result. In the cases of which we are now speaking we recognise the occurrence of lack of co-ordination in consequence of an abnormal amount of postural activity interfering with the normal peristaltic contractions. In such a case as this the

stronger of the two types of muscular activity will overpower the weaker—an occurrence which, in the case of voluntary muscles, would be certain to give rise to pain, and the degree of pain would be proportional to the force of the opposing types of muscular activity."

Stacey Wilson also says that the clinical aspects of this peculiar state of the colon wall were discussed at the International Medical Congress which was held in Paris in the year 1890, but I have not been able to verify this reference.

In addition to rest and the removal of any cause the most satisfactory method of treatment is by anti-spasmodic drugs, especially belladonna and hyoscyamus. All three of the cases described below were treated in this way. The pain gradually disappears and the hardening of the colon diminishes both in extent and degree, the iliac colon generally remaining palpable after spasm has disappeared from other parts of the large intestine. The condition has a great tendency to reappear and in some instances seems to be brought on by worry and overwork.

In Case 1 the pain and tenderness in the left iliac fossa were so marked, and the hardening of the colon was so striking, that at first I thought it possible that the patient was suffering from diverticulitis of the colon. An x-ray examination, made by Mr. Redding, both after a bismuth meal and an opaque enema, however, failed to show any diverticula, and the subsequent progress and history showed that the case was one of colospasm. The resemblance was, however, so striking that it raised the question as to whether there could be any connection between chronic spasm of the colon and the presence of multiple diverticula. The cause of the latter is still uncertain, though it is generally agreed that they are not congenital, but are the result of some form of distention of the bowel. Increased pressure within the bowel causing distention and stretching of all its coats would scarcely seem to be sufficient. It is true that a few cases have been recorded of diverticula having been found above a growth which is causing obstruction, but here there will also be muscular hypertrophy, that is hypertrophy and dilatation are both present. Is it not then possible, that in addition to increased pressure from distention, some other factor, some form of chronic muscular contraction or spasm is necessary? Under such circumstances one can understand that the lax mucous membrane, under pressure from within, might be forced through weak spots in the firm and contracted muscular coat. It has been pointed out<sup>6</sup> that the diverticula almost always take origin between the mesocolic and one of the lateral longi-

tudinal muscular bands, and frequently open into the appendices epiploicæ. Their situation appears to depend upon the anatomical distribution of the vessels, for numerous microscopical sections show the great frequency with which these sacculi push their way along the course of vessels, presumably weak spots.

This is a purely theoretical consideration, for though Mr. Redding has examined several of these cases for x-ray evidence of the presence of diverticula, in none as yet have any been found.

The following are notes of three typical cases, which illustrate most of the points raised in the present paper.

*Case 1.*—Lily P., aged 29 years, was admitted for abdominal pain in April 1921. In 1911 patient had been admitted into Miriam under Dr. French for pain in the region of the umbilicus of two years' duration. Four days after admission the pain was most marked over MacBurney's point, and a diagnosis of subacute appendicitis was made. Mr. Turner operated and removed the appendix, which was oedematous, with hæmorrhage beneath the mucous membrane.

Patient says that after the operation in 1911 the pain became better for a time, but soon returned and gradually became worse. The pain is of the same character and in the same place as it was before the operation. Pain has no relation to food and may occur at any time. Menstruation is regular and does not have any relation to the pain. There has been no vomiting, the bowels act well, and there has been no hæmorrhage per rectum. On examination the colon could be felt as a hard, rigid, tender structure as it crossed the left iliac fossa. The cæcum and the ascending colon were in a similar but less marked condition. The transverse colon could not be palpated, but there was tenderness across the abdomen below the umbilicus. Rectal examination showed no abnormality.

The tenderness and tumour in the left iliac fossa suggested the possibility of diverticulitis, and Mr. Redding sought for evidence of these both after a bismuth meal and an opaque enema. The report was that "The whole of the large gut filled rapidly; no stricture was seen, and no diverticula could be found."

She was treated with belladonna and hyoseyamus, improved and was discharged.

*Case 2.*—E. A. R., aged 40 years, was sent to me in 1919 with a history of numerous attacks of pain in the right iliac fossa, which appeared to be attacks of appendicitis. On examination it was found that patient had a right inguinal hernia, and that the right testicle was absent; the patient stated that the testicle had never been present in the scrotum. He had worn a truss since childhood, and the present instrument was perfectly comfortable and efficient. At the operation the appendix, which showed evidence

of old inflammation, was removed; a small atrophied testicle in the right iliac fossa in close proximity to the appendix was also removed through the same incision. The patient was again seen for abdominal pain three years later in August 1922. He had been relieved for a time, but the present pain, which the patient stated was of a different character from that of his original trouble, appeared some months afterwards. It had been much worse for the last five weeks, which increase was attributed to strain both physical and mental. The bowels acted normally; there was no vomiting; the pain was "gnawing" in character, and though it varied in intensity he was never free from it for a whole day and it often kept him awake at night. The pain had no relation to food, and was general but more marked on the right side. On examination the colon was hard and contracted as it crossed the left iliac fossa. The cæcum and the ascending colon showed the same change. There was also tenderness along the course of the transverse colon, though this part of the intestine could not be felt. The condition was considered to be one of spasm, and the patient was treated with belladonna and hyoseyamus. In a fortnight the symptoms were greatly improved and the spasm had almost disappeared. He was again seen in October 1923. He had remained practically well until last summer, when the symptoms recurred. On examination there was again evidence of spasm, the cæcum and ascending colon being chiefly affected, though there was also a slight degree of hardening of the iliac colon. The same treatment was adopted with almost immediate relief.

*Case 3.*—A man aged 25 was sent to me at out-patients in June 1921 with a suggested diagnosis of chronic appendicitis. For about six months he had suffered from abdominal pain, variable in position, but chiefly in the region of the umbilicus. The pain was "gnawing" in character, not constant, but lately had been felt nearly every day. The pain had no relation to food. There had been no vomiting; the bowels had been acting normally, and nothing unusual had ever been noticed about the motions.

On examination a remarkably hard and rigid colon could be felt in the left iliac fossa, and could be traced upwards nearly to the splenic flexure. In the right iliac fossa the cæcum and the ascending colon were in a similar condition. The transverse colon also could be readily palpated. The whole of the large intestine was tender, especially in the left iliac fossa. This patient was admitted for investigation, and after purgatives had been given without any effect on the spasm, Mr. Redding made an x-ray examination both after a bismuth meal and an opaque enema. No stricture of the colon was found and there were no diverticula.

The patient was treated with belladonna and hyoseyamus; symptoms rapidly improved and the hardening diminished, so that only the iliac colon could be felt, and that to a far less degree.

The patient remained well for a few weeks, but then the



symptoms recurred and the hardening reappeared, both on the right and left sides, though the transverse colon was now apparently not affected. He was again put on the same medicine, and while under observation both the symptoms and the spasm disappeared. He ceased to attend out-patients about the end of the year, and has not been seen since.

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## MYOMA OF THE STOMACH

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

INNOCENT tumours of the stomach are so very rare that they are apt to be mistaken for malignant disease before, during, and after operation. According to the statistics of the Mayo Clinic only 1 in every 200 gastric tumours is benign, and only 1 in 550 is a myoma. Between 1907 and 1921 2,168 patients were operated on at the Clinic for malignant disease of the stomach—2,146 for carcinoma, 20 for sarcoma, and 2 for malignant polyp. During this period there were only 27 operations for benign tumour.<sup>1</sup> In addition, however, 2,285 cases of inoperable malignant disease of the stomach passed through the Clinic, and it is of course possible that in some of these the growth was innocent and that an exploratory operation would have corrected the diagnosis. Several of the benign tumours were mistaken clinically for malignant disease and thought to be hopeless before operation, which was sometimes undertaken only at the earnest request of the patient.

The twenty-seven innocent tumours were divided as follows :

Myomas	.	.	.	.	.	10	} Generally submucous, sessile or peduncu- lated, and freely mov- able.
Fibromas	.	.	.	.	.	5	
Angiomas	.	.	.	.	.	4	
Dermoids	.	.	.	.	.	2	
Polyposis (Multiple papillomata)	.	.	.	.	.	1	
Adenomas	.	.	.	.	.	2	
Polyps	.	.	.	.	.	3	

During seventeen years as surgeon to Guy's Hospital the writer has met and removed only three innocent tumours of the stomach—one adenoma and two myomata. The main object of this paper is to contrast these two cases of myoma, and thus to show the importance of remembering the possibility of a gastric growth, although apparently hopeless, being innocent and curable by operation. In the first case, seen twelve years ago, the myoma was mistaken for sarcoma and partial gastrectomy performed in a very feeble, anæmic patient, with fatal result; in the second, seen this year, the tumour was at once recognised as a myoma and local resection successfully performed, although this patient was also very ill and anæmic before operation.

## CASE 1

George G., aged 49, was admitted to Guy's Hospital in September 1911 for abdominal swelling, melæna and wasting. Patient had first felt the swelling in March 1906, and about the same time blood appeared in his stools. He was admitted to the Hospital under Dr. Frederick Taylor for duodenal ulcer and treated for six weeks; he was then discharged apparently well. No tumour was noticed in the abdomen. On re-admission in 1911 a swelling could be felt  $1\frac{1}{2}$  inches above and to the right of the umbilicus. It was as large as an orange, freely movable and smooth on the surface. The patient did not vomit and had no pain or indigestion. He was very thin and extremely anæmic, having lost a great deal of blood per rectum, and having been kept for several weeks on a light diet for supposed duodenal ulcer. He still had severe melæna. Respiration was normal, but his pulse was feeble and rapid.

*Operation.*—Incision made to the right of the middle line and the stomach exposed. A large, soft, oval swelling was found in the pyloric part of the stomach. It was so freely movable within the stomach that it was at first thought to be a foreign body, but, on feeling it carefully, it was found to be attached by a broad pedicle to the posterior wall, near the lesser curvature and about three inches from the pylorus. A crater was felt at the summit of the tumour, easily admitting the tip of the thumb. The growth was thought to be malignant, probably a sarcoma, therefore partial gastrectomy was performed at once, nearly two-thirds of the stomach being removed and an anastomosis made between the remainder and the jejunum, after Billroth's second method. On examination the growth was found to be sub-epithelial, encapsuled, and had two excoriated deep ulcers on it. Microscopically it was a myoma.

The patient died exhausted four days after the operation, the exact cause of death being uncertain at the autopsy.

## CASE 2

David R., aged 67, was admitted to Guy's Hospital in April 1923 for pain and swelling in the left epigastrium and left hypochondrium. Seven weeks before, when getting up in the morning, the patient had a sharp attack of pain in the lower part of the left side of the epigastrium. The pain passed off in a few hours, but left an "ache" which continued for five weeks, when he had another attack of pain in the left side. He vomited twice during the day, on the first occasion bringing up a large quantity of black vomit; he felt weak, ill and faint and, for the first time, noticed that his fæces were black and liquid. The next two weeks he spent in bed feeling ill and giddy, and the motions continued black and loose. On examination in hospital the abdomen was found to be distended beneath

the left rectus, which was rigid so that no definite tumour could be felt. Later a very movable, cylindrical swelling was occasionally felt in the epigastrium, usually in the position of the transverse colon,  $\frac{1}{2}$  inch above and to the left of the umbilicus. It was tender on palpation and measured 3 inches transversely and  $1\frac{1}{2}$  inches vertically, but was most elusive, easily disappearing under the costal margin. Pulse 80, temperature 97, respiration 20. X-ray examination of the colon after barium enema did not show any evidence of obstruction of the colon. Chemical report of fæces: "Guaiac test positive. Hæmatoporphyrin well marked. No acid hæmatin. Altered blood present." It is probable that for some time past the patient had lost a great deal of blood by the bowel, for he was very pale and feeble. Diagnosis: Carcinoma of the colon was seriously considered, but the result of the opaque enema, the history of hæmatemesis and the great alteration of the pigments in the stools were in favour of a gastric lesion, probably carcinoma.

*Operation, 9.4.23.*—The swelling could not be felt under the anæsthetic. A left paramedian incision in the epigastrium revealed a swelling the size of a tennis ball inside the stomach, freely movable but attached to its posterior wall near the lesser curvature, a little to the right of the middle of the stomach. A crater could be felt in the globular swelling. A diagnosis of fibroma or fibro-myoma was made, and it was decided to remove it through the posterior wall of the stomach. An opening was made in the transverse meso-colon, and the swelling was then found to involve the wall of the stomach for about an inch. A pouch including the tumour was clamped off and an elliptical piece of the posterior wall removed with the growth, which was pedunculated and submucous, but had originated in the muscular coat of the stomach. The patient made a good recovery, and left hospital three weeks after the operation. He has remained well since.

*Pathological anatomy.\**—The growth was the shape of a hen's egg and the size of an orange. It was only attached to the stomach wall by a pedicle; its walls were thick and fibrous, but its centre was hollow, soft and hæmorrhagic.

After microscopic examination Dr. Nicholson reported the growth to be a fibro-myoma.

#### PATHOLOGY

Most innocent tumours of the stomach develop in the pyloric segment, either on the posterior or anterior wall, near the pylorus. They vary greatly in size, and are mostly sessile, but sometimes pedunculated and freely movable. Myoma starts in the muscular wall of the stomach, projects into the

\* This specimen was exhibited at a Meeting of the British Medical Association at Portsmouth in July, 1923.

cavity and, like the similar submucous growth of the uterus, is liable to injury from violent peristalsis and often degenerates, ulcerates and bleeds. The growth is rather soft, and may easily be mistaken for sarcoma until careful microscopic examination is made; even then the œdematous myoma removed from my first patient was thought to be a myxo-sarcoma. Myoma of the stomach is encapsuled and exhibits the characteristic arrangement of its large spindle cells. Sarcoma of the stomach is usually round-celled and infiltrating. In the Guy's Hospital Museum there are several examples of papillomata of the stomach of various sizes (Nos. 670 to 676), and one instance of a fibro-myoma (No. 678), the size of a pigeon's egg, which did not ulcerate or give rise to any symptoms.

#### SYMPTOMS AND SIGNS

Myoma, like other innocent tumours of the stomach, may give rise to no symptoms, but when it is polypoid it often causes vomiting, colicky pains from the engagement of the tumour in the pylorus, and sometimes intussusception of part of the stomach into the duodenum. A polypoid tumour may block the pylorus, as a large gall-stone often blocks the neck of the gall-bladder; it then acts as a ball-valve and causes intermittent pyloric obstruction with dilatation of the stomach and periodical vomiting. This occurs in about a quarter of the cases. Hæmorrhage occurs in about 37 per cent. of cases and is often very severe, as in the two cases recorded here. Ulceration or erosion and hæmorrhage may be partly due to violent peristalsis of the stomach. The appetite is generally good, but loss of weight is sometimes severe, amounting to anything from 10 to 60 lbs. A very mobile and elusive tumour may be felt in the epigastrium. The age of the patient varies very much, some being below the cancer age, but the majority well over 35. One of the most important clinical signs is defective filling of the stomach, as shown by radiography after a barium meal. It is usual for this defective filling to be globular and near the middle of the pyloric segment. Like the tumour, it varies greatly in size. The acidity of the gastric juice is usually normal or above normal, but there may be subacidity or achlorhydria, strongly suggesting malignant disease.

#### DIAGNOSIS

The common mistake is to diagnose the benign tumour as malignant. Any unduly movable tumour in the epigastrium,

especially if it disappears at times, should make us think of an innocent tumour or foreign body in the stomach. The long duration of the history with good digestive ability, normal or over-acidity of the gastric juice, with good general condition and sometimes youth, should tend to exclude malignant disease. Very profuse and repeated hæmatemesis is in favour of benign tumour, especially of hæmangioma or myoma; both my patients suffering from myoma nearly bled to death before operation.

On first feeling a movable tumour in the stomach during the operation, a foreign body, such as a hair-ball, suggests itself, but attachment to the wall of the stomach excludes this at once. Free mobility and absence of signs of infiltration are the most important indications of non-malignancy.

It is very difficult to distinguish between individual kinds of benign tumours, especially between angioma and myoma, for in both these hæmorrhage and a movable tumour are the most prominent features. In most cases the diagnosis will not be established until an operation has been undertaken. Angiomata are rarely felt clinically; when seen at the operation they are soft, spongy and bluish-black or red in colour. Multiple papillomata (polyposis) of the stomach occur in local collections and generally give a characteristic x-ray picture, the defective filling being partial or mottled on account of the barium insinuating itself between individual polypi, but this finding cannot be entirely relied upon. In two cases reported by Finney and Friedenwald<sup>2</sup> and in one by du Bray<sup>3</sup> the discovery on x-ray bismuth examination of a large clean-cut filling defect led to the diagnosis of carcinoma, but the correct diagnosis of innocent tumour was made at the operation and local removal successfully carried out. Achlorhydria, excessive peristalsis, and over-secretion of mucus are usually associated with this rare condition, which is variously described as inflammatory infective warts or adenomata. Occasionally, as in the case described by C. P. Mills<sup>4</sup> (when recording 18 others), multiple papillomata may be associated with carcinoma of the stomach.

#### OPERATION

When the condition is recognised, strictly local resection is the best and safest operation, there being no fear of recurrence if all the tumour is removed. To ensure complete removal, the whole thickness of the wall of the stomach is taken away with the tumour at its point of attachment.

## PROGNOSIS

A study of the recorded cases shows that an exploration of a gastric tumour is sometimes worth while even when the outlook seems to be hopeless. The results of operation for innocent tumour of the stomach have been extremely good, although in many cases of severe anæmia blood transfusion is necessary before operation.

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## PERFORATED JEJUNAL ULCER

By GRANT MASSIE, M.B., Surgical Registrar, Guy's Hospital.

THE prominent part played by gastro-jejunostomy in modern gastric surgery is responsible for the increasing frequency of secondary ulcers at or near the anastomosis. These ulcers may be gastro-jejunal, when they lie in the line of the anastomosis, or jejunal, when they lie in either the efferent or afferent limb of the jejunum, within, as a rule, an inch or two of the stoma. They may be acute, in which case the lesions are not uncommonly multiple, or chronic, in which case they are usually single. The clinical manifestations of such secondary ulcers are largely determined by their nature and situation and it is usual to recognise the following varieties :—

1. Those in which the first sign is acute perforation into the general peritoneal cavity. This complication is most common in the case of jejunal ulcer.

2. Those in which progressive chronic ulceration at the anastomosis leads to constriction of the stoma, with a recurrence of symptoms, somewhat resembling those for which the patient originally came under treatment.

3. Those in which chronic ulceration gradually penetrates the transverse mesocolon, resulting in a gastro-colic fistula. This variety of penetrating ulcer may also involve the anterior abdominal wall.

It is with the first group of secondary ulcers that this paper deals, namely, those in which perforation into the general peritoneal cavity is usually the first manifestation of their presence.

In reviewing the thirty-six cases of this lesion, collected from the literature of the subject and reported by various surgeons, it becomes evident in the majority of cases that the ulcer was situated in the jejunum and not at the anastomosis, and the acute perforation of a gastro-jejunal ulcer would seem to be an uncommon occurrence. Unless, therefore, this difference of behaviour can be explained by the situation of each it must be assumed that we are dealing with lesions of a somewhat different nature.

The case reported below is distinctly unusual in that two ulcers perforated simultaneously into the peritoneal cavity,



the first being an acute ulcer of the jejunum and the second a chronic ulcer at the anastomosis.

G. L., æt. 28, a clerk, was admitted to the hospital on May 6, 1923, at about 4.30 a.m., having been seized with a sudden and acute pain in the upper part of the abdomen about six hours previously. On inquiring into his previous history it was soon found that for several years past he had suffered from indigestion, for the relief of which a gastro-jejunostomy had been done at another hospital in December 1921. The indigestion of which he complained started in 1918, and at its onset was rather indefinite. In May 1919 he commenced to have attacks of pain in the right side of the epigastrium with periods of remission, until in January 1920 they became almost continuous. The pain at this time constantly appeared about two hours after food, and was always relieved by the next meal. During the following two months the pain gradually became worse, and about this time he started to vomit, although at no definite interval after meals. In November 1920 he was x-rayed, and a diagnosis of duodenal ulcer was made. He was then treated medically and towards the end of the year the pain gradually became less severe, and his condition so much improved that he discontinued treatment. This was followed by a relapse, and in May 1921 an operation was advised. The pain, however, again improved, and the operation was postponed, but in the latter months of 1921 his condition became worse and the vomiting was persistent.

In December 1921 a gastro-jejunostomy was performed, following which the pain completely disappeared, and the patient's condition greatly improved. This state of affairs continued until June 1922, when he was suddenly seized with an acute attack of pain, which lasted about two hours and appeared to have been similar to that for which he was admitted on the present occasion. As time went on these attacks gradually became worse and more or less continuous. The pain now usually came on immediately after food, and, starting in the upper part of the abdomen on the left side, radiated downwards towards the left iliac fossa. There was occasional vomiting. In October 1922 he was x-rayed, and the examination appears to have been satisfactory, for shortly afterwards he returned to work. The pain, however, persisted, and on a few occasions was so severe that he collapsed and had to be carried to bed. The last of these attacks previous to his admission occurred in April 1923.

On admission the patient presented the typical Hippocratic facies, but did not complain of pain. On inquiry it was found that shortly before admission his doctor had given him a grain of morphia. The abdomen was extremely rigid and somewhat distended. It was not tender, and did not move on respiration. Pulse rate was 118, and temperature 97°. A diagnosis of

perforated gastro-jejunal ulcer was made, and operation was immediately undertaken.

The abdomen was opened through a right paramedian incision, but not without some difficulty owing to the number of dense adhesions, and a quantity of yellowish turbid fluid immediately escaped, suggestive of duodenal contents. It soon became apparent that an anterior (antero-colic) gastro-jejuno-stomy had originally been performed, and that there were now two perforations, one in the anterior wall of the anastomosis and another in the afferent loop of the jejunum, about two inches away from the anastomosis. The first of these was partly sealed off by the adhesion of the liver to its upper part, and, although the ulcer itself was large, the perforation was relatively small. On turning to the second perforation, it was found to be about the size of a sixpenny piece, with sharply-cut edges, and without doubt an acute ulcer from which was escaping a rather viscid yellowish fluid. Both afferent and efferent loops of jejunum were greatly dilated.

Both perforations were rapidly sutured with two layers of catgut, and the abdomen was drained by a suprapubic incision. No difficulty was experienced in closing the jejunal perforation, but in dealing with the gastro-jejunal perforation it was found necessary to free the anastomosis from the liver before the suture could be satisfactorily introduced. The abdomen was rapidly closed in the usual way, and the patient returned to bed. During the following day the condition of the patient was critical, but improvement gradually followed.

During convalescence it was felt that further surgical treatment was advisable, without which it seemed likely that active ulceration would certainly recur. With a view to investigating the condition of the stomach and duodenum, a test meal was given, and Dr. Ryffel reported: "Marked regurgitation, as for gastro-jejuno-stomy, stomach emptying fairly rapidly."

On x-ray examination there appeared to be no evidence of gastro-jejuno-stomy, and food left the pylorus with fair rapidity. There was some deformity of the first part of the duodenum, and the stomach was practically empty in two hours.

Since it was evident that the pylorus was patent, and taking into consideration the considerable narrowing of the stoma, following the suture of the anastomotic ulcer, Mr. R. P. Rowlands decided to remove the anastomosis and restore the normal anatomy of the parts concerned. This was accordingly done at a later date, and at the same time the appendix was removed. The site of the previous jejunal perforation was identified, and this also was removed. The patient made an uninterrupted

recovery. An x-ray examination of the stomach before the patient left the hospital showed that only a very small trace of the meal remained after two hours. The test meal showed slight hyperchlorhydria.

*Comment.*—Six months after the gastro-jejunostomy symptoms appeared characteristic of secondary ulceration obstructing the anastomosis. The pain, originally most marked on the right side, moved to the left, appearing immediately after food and radiating towards the left iliac fossa. The acute attacks of pain were probably due to an impending perforation of the gastro-jejunal ulcer, which in the meantime had become adherent to the liver. Had the liver margin extended downwards for another centimetre, probably this perforation would never have taken place.

#### *Frequency of Perforation*

Regarding the frequency with which perforation ensues in a secondary ulcer, it is at present quite impossible to reach any satisfactory conclusion. The incidence of uncomplicated secondary ulcer is itself only a matter of conjecture, and beyond the fact that perforation would appear to be more common in the jejunal as opposed to the gastro-jejunal type of ulcer, no further conclusion can be drawn.

#### *Sex and Age*

Of the 37 cases reported the sex of 6 is not mentioned, but of the remaining 31 cases there were 24 males and 7 females. The youngest patient was aged two months and the oldest was 51 years. The average age of each was 35.2 years.

It will be noted that the preponderance of males over females, when considered with the average age of onset, is strongly suggestive in the light of modern knowledge, that the original lesion for which gastro-jejunostomy was performed was most commonly a duodenal ulcer.

#### *Situation and Nature of the Ulcer*

The perforation may be situated at the anastomosis or in the jejunum. In the latter situation it may be found either in the afferent, or more commonly in the efferent, limb of the anastomosis.

The situation of the perforation is not mentioned in 2 of the 37 cases reported. Of the remaining 35 cases 2 are of special interest in having had at different times two successive perforations. In the last case of the series the patient had a

double perforation. The situation of 38 ulcers, therefore, is recorded and is as follows :—

At the anastomosis . . . . .	8
In the jejunum . . . . .	30

In the majority of cases the ulcer was single, and in six cases only was more than one ulcer present. In five of the latter the lesions all occurred in the jejunum, and it is significant that in each of these perforation followed within a few days of the original operation, the shortest period being 5 and the longest 14 days. All these ulcers were therefore acute in origin and probably of what is commonly known as the septic type.

In the remaining case—No. 37—in which more than one ulcer was present, the one at the anastomosis was chronic; the other ulcer in the jejunum was beyond doubt acute. Turning to the small group of ulcers at the anastomosis, a consideration of the clinical histories would appear to show that complete relief did not as a rule follow the operation, and the reappearance of pain and discomfort in most leaves little doubt that most anastomotic ulcers which finally perforate are of the chronic type.

*Method of Gastro-jejunoscopy and the Interval before Perforation*

In one case the method of gastro-jejunoscopy is not mentioned. In the remaining cases it was as follows :—

ANTERIOR	{	Supra-colic . . . . .	1
		With entero-anastomosis . . . . .	3
		In Y. . . . .	2
		With partial gastrectomy . . . . .	1
		Simple . . . . .	14
POSTERIOR	{	With entero-anastomosis . . . . .	1
		Murphy button . . . . .	1
		With pyloric exclusion . . . . .	2
		Simple . . . . .	12

It will be noted that Schmilinsky, who excluded the pylorus in one of the two cases mentioned above, also performed in the same patient his own operation of “innere Apotheke.” In this operation the jejunum is divided transversely and the two ends are implanted separately into the posterior surface of the stomach, in order to ensure the regurgitation into the latter of the duodenal contents.

Regarding the interval between the original operation and the perforation of a secondary ulcer, it has already been pointed out that it is possible to recognise a small but definite group of acute cases in which multiple ulcers were present. In each case one or other of these ulcers perforated within 14 days of operation with fatal results. To this group must be added two further cases—Nos. 17 and 19 of the series—in each of which, although the lesion was single, it was in all probability acute, for in the first death took place with 10 days and in the second within 26 days of operation.

Turning from this group to a consideration of the remaining cases, it will be found that the average interval before perforation was about 2.6 years. If the cases of gastro-jejunal perforation are further separated from those in which the jejunum only was involved, it will be found that the interval in the two types of case differs only on the average by a few months.

It does not, however, necessarily follow that jejunal ulcers share the chronicity of those at the anastomosis, for it has already been pointed out that, whereas patients with the latter lesion usually complained of some symptoms suggesting unhealed or recurrent ulceration following operation, the patients with jejunal ulceration appeared to have recovered completely, and perforation was in almost every case the first evidence of an unsuspected lesion.

The conclusion therefore follows that jejunal ulceration is nearly always acute following an interval of supposed cure, or alternatively a chronic lesion which pursues its course without the slightest evidence of its presence. That the latter conclusion is unlikely is shown by a consideration of the following points. In the first place, although the nature of the ulcer is not mentioned in every case, in only a few is there any mention of the induration and contraction typical of chronicity, while the size and appearance of the perforation, on the other hand, in most cases strongly suggests an acute lesion. In the second place, while an ulcer at the anastomosis brings in its train renewed pain and discomfort, and finally leads to obstruction of the stoma, it seems almost inconceivable that a similar ulcer, when situated only an inch or so away in the distal jejunum, should give rise to an entirely different picture, in which perforation plays the leading part.

#### *The Method of Gastro-jejunostomy and its Relation to Secondary Ulcer*

Perforation of a secondary ulcer is a complication which may follow gastro-jejunostomy performed by any method, and is

not unknown even after partial gastrectomy. It is beyond doubt an uncommon complication, and probably many ulcers, especially those of the jejunal type, heal spontaneously with judicious after-treatment and never reach the stage at which perforation becomes possible. At the same time, in view of the interest attached to this rare catastrophe, it may be assumed that the great majority of cases have been reported, but when their total number is compared with the number of gastro-jejunosomies performed by every conceivable method since the introduction of the operation, it becomes evident that no accurate conclusion can be drawn as to the frequency with which this complication ensues.

It is commonly believed that anterior, as opposed to posterior, gastro-jejunosomy is more likely to be followed by secondary ulceration, and similarly that this risk is greater after operations of the Roux type, entero-anastomosis and pyloric exclusion. As far, however, as gastro-jejunosomy by the anterior method is concerned, this belief is by no means confirmed by a review of the cases at present under consideration, for, excluding methods other than simple anterior or posterior gastro-jejunosomy, it will be seen that there were 14 cases of perforation after the anterior, and 12 after the posterior method of operation.

Turning to the other methods of operation, it will be seen that in 4 cases entero-anastomosis was performed, but of a total of 37 cases this number would not appear sufficiently high to attract attention. At the same time entero-anastomosis enjoyed a vogue only in the earlier days of gastro-jejunosomy, when it was customary to use long jejunal loops which were very liable to become obstructed, and the number of occasions on which it was performed must necessarily have been small when compared with operations of the modern type.

On turning to pyloric exclusion, some surprise may be occasioned when it is seen that in only two cases of the series was the pylorus excluded at the original operation. Nearly every modern writer on the subject is of the opinion that pyloric exclusion is followed by secondary ulceration in a much higher percentage of patients than is the case in those in whom this measure has not been adopted, and it is indeed largely on this account that the operation has been generally abandoned. Why, then, is acute perforation uncommon as a sequel to an operation in which the incidence of secondary ulceration is notoriously high?

It has been shown above that perforation of the anastomotic type of ulcer is much less common than perforation of the jejunal type of ulcer, for of a total of 38 perforations 8 only were of the

first type, while the remaining 30 were of the second type. The conclusion would therefore appear to be that pyloric exclusion leads more often to a chronic anastomotic ulcer, whose tendency to perforate is slight, and it is doubtful whether secondary ulcer in the jejunum is more common after this than after any other operation.

In conclusion, an attempt has been made to show that jejunal ulcer is a definite entity, differing from the gastro-jejunal ulcer in several respects. It has been shown that of perforated secondary ulcers, those in the jejunum are most common, appearing and perforating without warning. This behaviour offers a marked contrast to that of the anastomotic ulcer, of which the course is chronic and the tendency to perforate slight. It has been suggested by some writers that an ulcer in the jejunum is an extension from an ulcer at the anastomosis, but this is probably not often the case, and in the last case of the series, in which an ulcer of both types was found, the jejunal mucosa separating them was perfectly normal. In further support of the acute course of jejunal ulcer, it might be expected that perforation would much more commonly occur when the anastomosis lay anterior to the stomach, for the same reason that perforated gastric ulcer is more commonly anterior than posterior, but such, however, is not the case, and the course of a jejunal ulcer is not modified by its deeper situation.

Jejunal ulcer and perforation may follow gastro-jejunostomy performed by any method, even the most modern, and there does not appear to be sufficient evidence to attribute its causation to the method of anastomosis. On the other hand, while gastro-jejunostomy leads to a permanent cure in the great majority of patients with duodenal ulcer, there appears to be at the same time a small but distinct group in which the tendency to ulceration is so extreme that the operation, although relieving the original condition, leads to sequelæ of greater severity. In these patients it may be assumed that the underlying cause of the lesion is neither discovered nor treated, and the cure is worse than the disease. Unfortunately at present there are no means at hand for the identification of these patients, but in all cases gastro-jejunostomy should not be considered the only step in their treatment, every attempt should be made to eradicate septic foci, and medical treatment should be continued after operation.

I am indebted to Mr. R. P. Rowlands for his kind permission to publish the case here reported.

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No.	Recorder.	Age and sex.	Method of Gastro-jejunostomy.	Interval between operation and perforation.	Situation of perforation.	Treatment.	Result.
1	Braun.	M. 25	Posterior.	12 months.	Jejunum, efferent limb 1" below anastomosis.	No operation.	Death.
2	Hahn.	M. —	Anterior.	1 year.	Jejunum, efferent limb 1" or 2" below anastomosis.	No operation.	Death.
3	Korte.	M. 30	Anterior.	3 years	Jejunum, 7 cm. from anastomosis, subacute perforation, subphrenic abscess.	Laparotomy.	Death.
4	Steinthal.	M. 44	Posterior (Murphy button).	10 days.	Jejunum, 2 in afferent and 2 in efferent limb.	No operation.	Death.
5	Goepel.	—	Anterior.	13 months.	Jejunum, adjoining anastomosis.	No operation.	Death.
6	Goepel.	—	Anterior.	4 months.	Jejunum, adjoining anastomosis.	Suture.	Recovery.
7	Brentano.	F. 26	Anterior, Entero-anastomosis.	1 year.	Anastomosis.	Suture.	Recovery.
8	Cackovic.	M. 30	Posterior.	5 days.	Jejunum, 4 ulcers in efferent limb, one opposite and one 15 cm. below.	No operation.	Death.
9	Goepel.	M. 34	Anterior.	9 months.	Jejunum, site not stated.	Suture.	Recovery.
10	Mikulicz.	F. 2 mons.	Anterior, Entero-anastomosis.	2 weeks.	Jejunum, ascending limb, several other ulcers near anastomosis.	No operation.	Death.
11	Dudgeon and Sargent.	M. 30	—	22 months.	Jejunum, close to anastomosis.	Suture.	Recovery.
12	Battle.	M. 30	Anterior.	22 months.	Jejunum, immediately below anastomosis.	Suture.	Recovery.
13	Battle.	F. 37	Anterior.	(a) 1 year.	(a) Jejunum 1½" from anastomosis.	(a) Suture.	Recovery.
14	Delaloye.	M. 41	Anterior.	(b) 2 years.	(b) Anastomosis.	(b) Suture.	Recovery.
15	Graser.	F. —	Posterior.	6 years.	Anastomosis, near afferent limb.	No operation.	Death.
16	Edington.	M. 39	Anterior.	3 years.	Anastomosis.	No operation.	Death.
17	Hamann.	M. 48	Anterior, Entero-anastomosis.	7 years.	Jejunum, descending limb, close to anastomosis.	Suture.	Death.
18	Hybrinette.	F. 45	Anterior, Entero-anastomosis.	26 days.	Jejunum, efferent limb, just beyond anastomosis.	No operation.	Death.
19	Lenander.	F. 25	Anterior in Y.	7 years.	Anastomosis, ulcer constricting the stoma.	Suture.	Recovery.
			Anterior, Partial Gastrectomy.	10 days.	Jejunum, site not stated.	No operation.	Death.

No.	Recorder.	Age and sex.	Method of Gastro-jejunostomy.	Interval between operation and perforation.	Situation of perforation.	Treatment.	Result.
20	Paterson (Hall).	M. 48	Anterior Supra-colic.	2 years.	Jejunum, 6" below anastomosis.	No operation.	Death.
21	Paterson (Parker).	M. 51	I. Pyloroplasty, Anterior. II. Gastrojejunostomy.	2½ years.	Jejunum, opposite anastomosis, ulcer indurated.	No operation.	Death.
22	Eiselsberg.	M. 40	Posterior, Pyloric Exclusion.	2 months.	Under the anastomosis.	Suture.	Death.
23	Maylard.	F. 51	Anterior.	(a) 8 months. (b) 2 years later.	(a) Jejunum, efferent loop. (b) Jejunum, just below above.	(a) Suture. (b) Suture.	Recovery.
24	Petrén (Barrhjem).	M. 37	Posterior, Entero-anastomosis.	10 months.	Anastomosis, left extremity.	Suture.	Recovery.
25	Petrén (Euren).	M. 18	Posterior.	6 days.	Jejunum, 2 ulcers in afferent loop, one perforated.	No operation.	Death.
26	Hitzrot.	? 26	Anterior in Y.	9 years.	Jejunum, opposite anastomosis.	Suture.	Recovery.
27	Movnhan (Norman Porrit).	M. 29	Posterior.	7 days.	Jejunum, opposite stoma. Another ulcer on lesser curvature was found.	Suture.	Death.
28	Hartmann (Marquis).	M. 41	Posterior	6½ years.	Anastomosis, nearer jejunum than stomach.	Suture.	Recovery.
29	Rowlands.	—	Anterior.	5 years.	Jejunum, 1" below anastomosis.	Suture.	Recovery.
30	Schmilinsky.	—	Posterior.	22 months.	Jejunum.	Suture.	Recovery.
31	Schmilinsky.	—	Posterior, Pyloric exclusion. "Innere Apotheke."	17 months.	Jejunum, afferent loop of "Innere Apotheke."	Operation not described.	Death.
32	Pólya.	M. 36	Posterior, Short loop.	10 months.	Jejunum, opposite anastomosis.	Operation not described.	Death.
33	Brütt.	M. 40	Anterior.	6 years.	Jejunum, efferent limb.	Suture.	Death.
34	Brütt.	M. 18	Posterior, Long loop.	3 years.	Jejunum, exactly opposite anastomosis.	Suture. New anastomosis proximally.	Recovery.
35	Haberer.	M. 40	Posterior.	4 weeks.	Not mentioned.	Suture.	Death.
36	Haberer.	M. 34	Posterior.	3½ years.	Not mentioned.	Suture. Jejunostomy.	Death.
37	Massie.	M. 28	Anterior.	16 months.	I. Anastomosis. II. Jejunum, afferent loop, 1-2" from anastomosis.	Suture.	Recovery.

## STUDIES ON TUMOUR FORMATION

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### VIII. THE MIXED TUMOURS

THE essential cells of a tissue or organ are known as its *parenchyma*. It is they that possess the structure characteristic of and necessitated by the performance of its functions. The parenchyma consists of epithelial or of mesenchymal cells, or of both; these may be of one or of several kinds. Thus, that of an artery comprises endothelium, fibrous and elastic tissue and plain muscle. These tissues are supported, nourished and controlled by areolar tissue, capillaries and nerves, which together are spoken of as the *stroma*.

But the distinctions between the parenchyma and the stroma of an organ are often not as sharp as we might be led to suppose. The liver, for instance, contains secreting acini and bile-ducts; these clearly constitute its parenchyma. They are supported by Glisson's capsule with its vessels and nerves; these are equally obviously its stroma. But the liver is essentially a vascular organ, whose lobules are permeated by a network of blood spaces, the ramifications of the portal and hepatic vessels. They do more than provide an adequate blood supply, and the liver could not functionate without them. They are therefore necessary for the performance of its physiological action, and must be regarded as part of its parenchyma.

Again, is not the capsule of Glisson, that we have defined as stroma, with its characteristic dense structure, as essential for the liver as its parenchyma? If it were not, it would assuredly not be there. It must be as important as the plain muscle of the prostate which, since this tissue is not of ubiquitous occurrence throughout the body, we are inclined to consider as part of the parenchyma of that organ.

Yet again, the architecture of the stroma is every bit as characteristic for all the tissues of the body as that of their parenchyma. It varies enormously in different organs in bulk, density and vascularity. It is generally taught that the epithelium of an organ exerts a moulding or directing influence upon the stroma. This is no doubt true, in part at least. At all events it shows that a certain balance between epithelium

and stroma is set up and must be maintained if physiological activity is to take place.

We have seen that tumours do not differ in their fundamental structure from other tissues. They possess a stroma as well as a parenchyma. The former is as characteristic as that of normal organs in the different kinds of tumours in respect of bulk, density and vascularity. Nothing, for instance, could be more constant than the scanty stroma of villous papillomata of the bladder, which consists of little else than thin-walled blood-vessels whose coats are often hyaline, or than the dense fibrous stroma of the commonest forms of carcinoma of the breast.

I need not emphasise that constancy of type is the most characteristic feature of the parenchyma of tumours. Our classification depends upon it. The parenchyma of a neoplasm usually consists of one physiological type of cell only. Occasionally, however, it is built up of two or more tissues. These may be derivatives of one, two, or all the germinal layers. In the last case we speak of a teratoma.\* With certain exceptions all the remaining tumours with more than one parenchyma may be grouped together under the heading of Mixed Tumours.

*Tumours with a Two-fold Stroma.*—Since in accordance with our definition a mixed tumour contains more than one kind of parenchyma, it follows that all neoplasms must be excluded from this group in which the stroma consists of more than one tissue. It is easy in most cases to distinguish the stroma from the parenchyma of a tumour, since the former, however abundant it be, can be shown to be directly continuous with and a part of the stroma at the periphery of the neoplasm. The mesenchymal parenchyma of a tumour is, on the other hand, always more or less isolated from its surroundings, unless it possesses malignant characters and infiltrates them as a sarcoma. Thus, the "ossifying epitheliomata" of the skin (Hutchinson<sup>12</sup>) and of the infundibular process of the pituitary (Erdheim<sup>5</sup>) are not mixed tumours, in spite of the fact that they contain bone and red marrow, since these heterotopic structures are to be explained as depending upon inflammatory processes set up in the stroma of the neoplasm after death and calcification of the cells of its parenchyma.<sup>19</sup>

The specimen † reproduced in Fig. 77 can perhaps be explained upon somewhat similar lines. It represents a carcinoma of the prostate, whose shrunken alveoli are surrounded

\* Teratomata occasionally contain derivatives of only two or even one germinal layer. In other respects, however, they agree with the "tri-dermal" teratomata, and are best discussed with these.

† I am indebted for it to Dr. J. R. Perdrau, of the Lambeth Infirmary.

by cellular connective tissue containing numerous trabeculae of osteoid tissue and calcified bone. The drawing demonstrates that these heterotopic tissues were laid down by the cells of the granulation tissue. This specimen differs from the ossifying epitheliomata alluded to above in that no areas of necrosis and of calcification of the epithelium or of a part of the stroma are present. The granulation tissue shown in the figure passes into the general stroma at the edges of the new growth. It is clearly the stroma of the latter and not one of its essential constituents. No post-mortem examination was performed.

An almost identical case has been described by Gruber,<sup>9</sup> who found bone in the stroma of a carcinoma of the stomach.

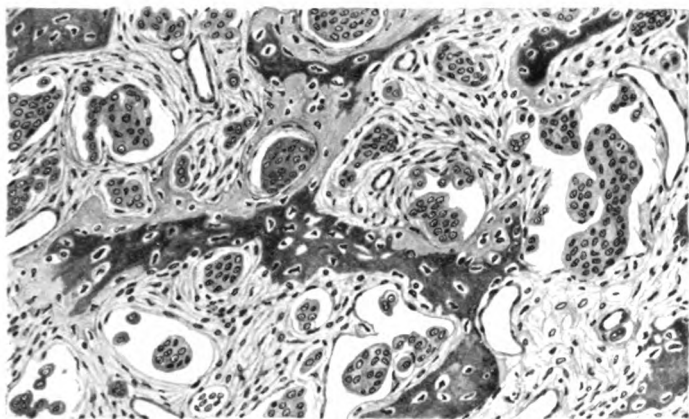


Fig. 77.

“Metastatic” ossification of stroma of carcinoma of prostate. Magnif., 180.

It had been deposited by osteoblasts as well as by direct conversion of the cellular connective tissue. There was extensive calcification of the arteries of the body, but the bones were not examined.

It is much to be regretted that no examination of the skeleton or the kidneys was made in either of these cases, since they appear to me to be closely related to the condition described by Virchow<sup>26</sup> as “Calcium metastasis.” This condition is characterised by calcification of the lungs, the mucous membrane of the stomach and, to a lesser extent, of other organs in cases of new growth with large secondary deposits in the bones. The kidneys were diseased in every case. His explanation of this condition is that large quantities of calcium salts entered the circulation, having been set free by the absorption of bone produced by the secondary deposits, aided by defective excre-

tion of the diseased kidneys. The body thus became supersaturated with them, and they were precipitated in those tissues in which a considerable amount of acid is liberated and removed, *i. e.* the lungs and the gastric mucous membrane.

Gruber<sup>9</sup> explains his case upon the assumption that the young connective tissue that proliferated in the stroma of the tumour had a particular affinity for calcium salts and combined with them to form bone. He cannot say if the necessary salts were set free because of rarefaction of the skeleton by secondary deposits, or because of some anomaly of calcium metabolism, since a complete autopsy was not allowed.

The calcium salts that circulate in the body are kept in solution mainly by  $\text{CO}_2$  (Hofmeister).<sup>11</sup> This substance is constantly liberated and removed in the lungs, with the result that the pulmonary tissues tend to be alkaline.  $\text{HCl}$  is constantly excreted by the mucous membrane of the stomach, whose tissues therefore likewise tend to be alkaline. The calcium salts circulating in these tissues therefore tend to be precipitated. Should there be a general supersaturation with calcium salts; they are actually precipitated in these regions, as was pointed out by Virchow.<sup>26</sup> The same arguments apply to the calcification of necroses and of non-cellular sclerotic fibrous tissue. Here metabolism is entirely absent or extremely low. A minimum of  $\text{CO}_2$  is given off, the tissues tend to be alkaline, and precipitation of calcium salts is induced.\*

The granulation tissue constituting the stroma of our carcinoma of the prostate is very cellular. Its metabolism must therefore have been active, its respiratory interchange high, and a large amount of  $\text{CO}_2$  must have been given off. Even though we assume, for the sake of argument, that the calcium content of the blood was abnormally high in this case, we should expect these salts to remain in solution here if anywhere in the body. And this is actually the case. There is no evidence of calcification of the fibrillar stroma of the granulation tissue even in its densest parts. This process is entirely and absolutely limited to the newly formed bone. In other words, instead of a pathological calcification we have here a physiological ossification. Osteoid tissue has been laid down, and this alone has undergone calcification into bone.

The processes that have ended in the production of bone in the stroma of our tumour of the prostate appear to me to be

\* However quickly and efficiently the alkalinity of the body be regulated, it is evident that a tissue in which  $\text{CO}_2$  is constantly being liberated without being instantly removed must be more acid than one in which no liberation takes place.

strictly comparable with those that are at work in physiological "ossification in membrane." The sole difference is that, whereas in the latter case this process is confined to certain definite regions, it has in the former taken place in an abnormal situation. The bone is heterotopic. We can therefore dismiss the actual phenomenon of calcification, since it has its physiological prototype, and is to be explained in precisely the same way, although it may at first sight appear to violate the laws of chemistry. We must leave the elucidation of this question to physiologists, be the answer a "physiological or vital disposition" of osteoid tissue to undergo calcification and by doing so to become bone, or be the explanation a more tangible one. Here we need only try to find a rational explanation for the presence of osteoid tissue in an abnormal or heterotopic situation.

I<sup>19</sup> have tried to explain the presence of the bone frequently to be seen in and around calcified necrotic tissues as a physiological reaction of the cells of the granulation tissue that has invaded these lesions to the local supersaturation with calcium salts resulting from its own erosive activity. This process is entirely comparable with the physiological endochondral ossification of the skeleton. I assumed, upon evidence which appears to me to be adequate, that the cells of active young granulation tissue are practically undifferentiated, and that the course their differentiation pursues depends principally, if not entirely, upon their environment. Should they be exposed to a local excess of calcium salts in solution, they must undergo it in the same direction as in the developing skeleton, and take on the functions and the structure of bone-forming cells. I do not see why this should not be true in the case of a general supersaturation with calcium salts, as in Virchow's<sup>26</sup> "metastatic calcification." I assume that the cells of the granulation tissue react or adapt themselves to the abnormal environment in the only way possible for them. They secrete an osteoid matrix which, from its very nature, takes up calcium salts and becomes true bone.

Indeed, heterotopic ossification of granulation tissue, granted the presence of a general excess of calcium salts, appears to me to be far more readily comprehensible than physiological "ossification in membrane," where no such abnormality can be assumed. Again, may it not be a protective mechanism, physiological in that it tends to diminish the concentration of the calcium salts in the circulation, and pathological only in that its amount is totally inadequate to attain this result?

It will be urged against me that, as no post-mortem examina-

tion was performed on the cases described by Gruber<sup>9</sup> and by me, I have no evidence of the state of the skeleton or the kidneys, and that the whole of my theorising is based upon foundations no more solid than speculation. I am fully alive to the truth of this objection. These cases appear to be very rare, and I may never see another. I have therefore ventured to speculate in the hope of inducing others who may meet with one to carry out full investigations of its calcium metabolism during life, as well as a complete post-mortem examination. At its worst, my speculative explanation is no more so than the alternative

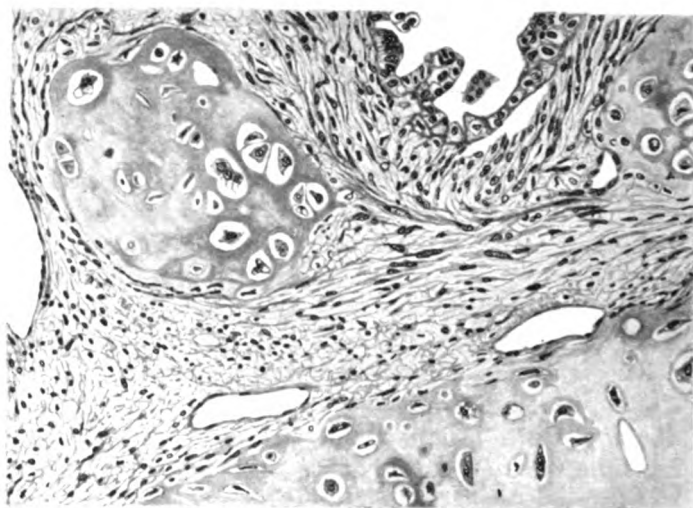


Fig. 78.

Nodules of hyaline cartilage in stroma of carcinoma of body of uterus.  
Magnif., 180.

empirical one of an "abnormal predisposition" of the stroma for bone formation.

Fig. 78 represents the malignant granulations that lined the uterine cavity in an extensive columnar-celled carcinoma of the endometrium. The periphery of the neoplasm is very cellular, with active infiltration of the muscle. Here the stroma is minimal and limited to an occasional connective tissue fibril between the epithelial cells, as well as numerous capillaries. As the central parts of the tumour that form a lining to the uterine cavity are reached, the fibrous stroma is gradually increased in amount and in cellularity. Its cells are soon separated by a granular matrix, which takes on the staining-reactions of mucin. In this part of the specimen the blood-vessels are relatively few in number, being generally represented



by wide, thin-walled sinuses. Areas are to be seen everywhere in the mucoid stroma in which the cells are enlarged and occupy spaces in the interstitial substance. This has here become homogeneous and glassy. It is frequently condensed around individual cells or groups of cells as capsules. These areas possess all the characters of hyaline cartilage. Large nodules of this tissue are present almost everywhere. Many of them show evidence of interstitial growth, since they are surrounded by concentric, evidently compressed layers of connective tissue. The drawing shows nodules of hyaline cartilage, many of whose cells present the swollen and vacuolated bodies and nuclei characteristic of this tissue.

I claim that this is a clear case of the conversion of the cells of the fibrous or areolar stroma of a carcinoma into hyaline cartilage, by way of oedema and mucoid degeneration. The latter changes I explain as depending upon circulatory disturbances set up by the want of an adequate blood supply, and by the pressure in the central parts of the tumour. Since the stroma of the neoplasm is derived from that of the surrounding tissues, we have here an instance of the conversion or heterotopic differentiation of the connective tissue of the uterus into hyaline cartilage. It is caused by the new or abnormal environment. I believe that the case under consideration is strictly comparable with the instances of heterotopic cartilage I have discussed upon pp. 353 to 356 of the third of these studies. It appears to me to furnish strong evidence that this tissue, when met with in unusual situations, can readily be accounted for as an anomaly of differentiation of the cells of the part, and that the assumption of an included mesodermal cell rest or an abnormal predisposition of the stroma is unnecessary.

In the specimen under discussion many of the nodules of cartilage show distinct signs of independent proliferation. They are slight, however, and strictly within physiological limits, and cannot be called blastomatous. The question arises if it be possible for the cells of the stroma of a tumour to undergo blastomatous growth and to proliferate indefinitely side by side with its parenchyma as a mixed tumour. I believe this to be possible, and have described a tumour of the body of the uterus with areas of chondro-carcinomatous tissue upon these lines.<sup>20</sup> The whole question will have to be gone into fully when we come to discuss the carcino-sarcomata.\*

*Osteo- and Chondro-sarcomata.*—Another class of neoplasm should be distinguished from true mixed tumours. I refer to the osteo-sarcomata of the skeleton, in which the newly deposited

\* See Appendix at end of this paper.

bone is the result of a process of differentiation of the cells of the sarcomatous parenchyma of the new growth. There can be no question that these tumours originate in the periosteum and the endosteum, whose principal physiological function it is to supply the new bone required during the period of growth, and in later life to produce the absorption and the appositional new growth responsible for the moulding process to which the bones are constantly subjected.

Closely allied to the osteo-sarcomata are the chondro-sarcomata of the skeleton. Those found in the epiphyses and near the joints are no doubt derivatives of the perichondrium. But these tumours are to be met with in the shafts of bones, where no cartilage is present in the adult. Nevertheless, they do not necessitate the presence of displaced islands of cartilage to be explained, since it is a well-known fact (Kapsammer)<sup>13</sup> that cartilage makes its appearance in the callus of fractures, especially when there is a high degree of mobility of the fragments. Since the cells of the endosteum and the periosteum give rise to cartilage in repair, it need not surprise us that they should do so in new growths.

Cartilage and newly formed bone often occur side by side in the parenchyma of these sarcomata of the skeleton, as the result of differentiation of its cells in both these directions. In most of the osteo-chondro-sarcomata that I have examined there is no evidence of replacement of the cartilage by bone, such as we see in physiological endochondral ossification. Nor have I seen evidence of the direct conversion of cartilage into bone. The appearances point to the fact that some of the sarcomatous parenchyma cells undergo differentiation into cartilage, and others into bone.

The structures found in these tumours represent the final stages of differentiation of the cells of their tissue of origin. They are produced by a process of physiological maturation or ageing which is common for all tumours. I therefore do not include them with the mixed tumours.

The same considerations apply in the case of the corresponding innocent tumours, the chondromata that have undergone a physiological process of calcification and endochondral ossification. The bone is practically always deposited by appositional growth of cells that correspond in function, and usually in their typical structure, with osteoblasts. Lamellar bone is laid down and replaces the cartilage, whose cells are dead or dying. The cells that produce bone are derivatives of the endosteum that forms a cloak around the blood-vessels which have invaded the cartilage where it has undergone calcification.

I do not know whether this tissue is one of the original components of the tumour in an altered form, or if it invades it from the surrounding marrow with the blood-vessels. But this does not seem to me to matter, since the whole process, be it a substitution of one kind of parenchyma cell of the tumour by another, or be it a replacement of the tumour by the tissues of the skeleton, is clearly one of physiological differentiation. I therefore exclude these ossifying chondromata from the group of mixed tumours.

I do not include even the circum-articular exostoses of young subjects in this group; they are capped by a zone of hyaline cartilage throughout their period of growth. Its inner edge undergoes typical endochondral ossification, which keeps pace with the new formation of cartilage by proliferation of its peripheral cells. The bony tissue thus produced is joined with that of the shaft of the bone, and its red and fatty marrow communicate with the marrow spaces of the latter. These exostoses are of interest, since they are tumours and accessory diaphyses. They are splendid examples of hamartomata or tumour-like malformations. They are tumours only because they grow in bulk and thus give rise to a mass of bone where this is normally absent.

1. *Fibro-adenomata of the Breast*.—Now that those tumours whose stroma consists of more than one kind of tissue have been excluded from the group of mixed tumours, as well as those whose parenchyma has given rise to more than one tissue by a process of physiological differentiation, we turn to the consideration of the proper subject-matter of this study. We shall find that mixed tumours are a heterogeneous group, that they vary greatly in structure in different parts of the body, are built up of a great variety of tissues, and present wide differences in their rate of growth and clinical behaviour. We shall find too that their histogenesis is a varied one, which we shall try to explain in many different ways. We will begin with the simplest, commonest and best-known of them, the fibro-adenomata of the mammary glands.\*

These tumours are isolated from the substance of the breast and usually well encapsulated. They often present an uneven, nodular surface. In rare cases they are extensively branched. They are first met with in young women, in the years succeeding puberty. They are rarely, if ever, found in children. Bland-Sutton <sup>24</sup> (p. 807) writes about them :

\* I am not dealing here with the so-called cyst-adenomata, intra-cystic papillary adenomata, or duct-papillomata.

The great rarity of fibro-adenomas of the breast before puberty is due to the simple construction of the breast in the non-pubic girl. The gland-elements are represented by epithelium-lined tubes, which branch slightly, embedded in fibrous tissue. After puberty the gland-elements multiply, and this activity is accompanied by a corresponding active growth of the fibrous tissue of the breast.

I add to this that fibro-adenomata are to be found in breasts which otherwise show no abnormality, especially in youthful subjects. I must, however, admit that, since they are almost always well encapsulated, and even have a marked tendency to be extruded into the wound when the neighbouring tissues are incised, they are, quite properly, simply removed with their capsule, and that I have never had the opportunity to examine the mammary tissues at a distance from the tumour. A breast which is the seat of a fibro-adenoma in older women often presents the picture of chronic mastitis, apart from the changes in the immediate neighbourhood of the tumour due to pressure.

Two types of fibro-adenoma mammae are to be distinguished histologically, connected though they be by innumerable intermediate stages. These are the so-called peri-canalicular and intra-canalicular varieties. They are both built up of epithelium and connective tissue, and thus possess a double parenchyma, partly epiblastic and partly mesenchymal. They are therefore mixed tumours in accordance with our definition of the term. The connective-tissue parenchyma varies enormously in amount, in cellularity, in density, and in the arrangement of its fibres. It usually reaches its maximum of development and cellularity in the intra-canalicular growths. Here it forms nodules and complex irregular proliferations, which press upon, partially invaginate and distort the epithelial tubules. These proliferations are generally very loose in structure, and consist of cellular areolar tissue with spindle-shaped and stellate cells, closely resembling the intra-lobular connective tissue of the breast. Strands of coarse dense fibrous tissue are present as a rule. They separate the tumour into irregular lobules, which are often incomplete. A striking, although distorted resemblance to those of the breast is thus maintained. The epithelium forms groups of acini which resemble those of the normal gland more or less closely in the peri-canalicular variety, but are pulled out into long tubular cracks or spaces in the intra-canalicular forms. Its rate of growth generally keeps pace with that of the connective tissue, but signs of proliferation are commonly met with. This is either external, into the connective tissue, in the shape of buds and acini, or internal, into

the lumen of the tubules, which thus become blocked by solid columns of cells, or filled with papillomatous projections.

I must add, to complete this brief histological description, that Cheatele<sup>4</sup> has divided the fibro-adenomata into those of the "intra- and extra-elastica" type. He shows that the elastic coat of the ducts and acini of the breast is separated from the epithelial structures by a thin layer of delicate connective tissue, whereas the loose intra-lobular fibrous tissue binding the acini of a lobule together lies outside the elastic coat. He finds that some fibro-adenomata are completely inside the elastica, whereas in others the epithelium of the tumour is separated from the bulk of its connective-tissue parenchyma by this layer.

So much for the histology of these tumours. Every attempt to explain their histiogenesis must take into account the double nature of the parenchyma, its epithelial and its mesenchymal moieties. The former is clearly derived from the secreting parenchyma of the breast, whereas the latter is a derivative of its stroma, more especially of its intra-lobular connective tissue. This twofold origin of the parenchyma has given rise to doubts in the minds of pathologists concerning the histiogenesis of these tumours, with the differences of opinion that are their inevitable consequence.

Different specimens of fibro-adenoma present enormous variations in the amount of proliferation of their epithelial parenchyma. In many of the peri-canalicular forms it is present in a degree which may well be described as dominant. But in others, more particularly in the intra-canalicular types, the connective tissue is obviously the active partner, which moulds and distorts the epithelium into the most bizarre shapes. Since a "peri-canalicular" structure is often present in parts of intra-canalicular tumours, especially at their periphery, it might be urged that the enormous growth of the connective tissue is a secondary process in these cases, and that all fibro-adenomata begin their independent existence as peri-canalicular growths. The new growth of the connective tissue might be regarded as of the nature of a secondary hyperplasia, induced in some way by the epithelium. But this idea is inadmissible. I have described and figured (II. Figs. 35 and 36) two small hamartomata that I regard as young examples of the two types of fibro-adenoma. In many intra-canalicular tumours the growth of the connective tissue is so excessive that the epithelium is not uncommonly atrophied and squeezed out of existence by it. Does this process differ from those commonly seen in chronic inflammations with hyperplasia of the stroma of an organ and

atrophy of its epithelium? Assuredly, since in our case it is autonomous, blastomatous, and, as far as we know, quite independent of its surroundings. Again, there are many intra-canalicular fibro-adenomata that are clearly primary formations, and in which the assumption cannot be made that they have started life as peri-canalicular growths. Nor can we assume that these tumours are simply fibromata in which epithelial proliferation of accidentally included tubules manages to keep pace with that of the connective tissue. The buds and groups of acini given off in nearly every peri-canalicular fibro-adenoma preclude this view. We are forced to assume that the epithelium and the connective tissue possess a more or less independent rate of growth, and that in some cases the one, and in others the other assumes dominance, but that they are both essential constituents of the parenchyma of these tumours.

We know that nearly every tumour, once it has attained the status of one, grows solely by proliferation of the cells of its parenchyma. The so-called "transitional" changes in the epithelium in the immediate neighbourhood of a carcinoma are not true transitions, in the sense of early malignant changes, but almost invariably due to inflammatory hyperplasia and secondary unions between the cells of the tumour and those of the regional epithelium. So universally does this rule apply that it has been elevated to the dignity of a law by Ribbert,<sup>22</sup> who maintained that no tumour, however small, in any circumstances whatever, receives additions to its mass from without.\* If we believe, with Ribbert, that the growth of tumours is always closed and independent of the surroundings for reinforcements, it becomes very hard to explain the histiogenesis of a neoplasm whose parenchyma consists of two or more discrete tissues, one of which, in the cases under discussion, is a derivative of the epiblast, and another of the mesenchyme. If we attempt with Ribbert to visualise the earliest stages of such a mixed tumour, we fail to see how it is possible for its earliest rudiment or "germ" to have been other than compound. If we were to assume that the neoplasm has originated in epithelium, in accordance with the view generally held by embryologists that this tissue exercises a dominant or moulding effect upon the subjacent mesenchyme in organogenesis, how can it have induced the mesenchyme to join hands with it to form one of its integral parts? It is quite as difficult and far more distasteful to postulate a primary dominance of the mesenchyme. If we follow Ribbert we are bound to postulate that the rudiment or germ of the tumour was compound from the very beginning,

\* I have discussed this question upon p. 41 of Study V.

unless we assume a purely hypothetical process of infection with neoplastic characters of one kind of tissue by the other.

It has thus come about that the view has been almost universally accepted that mixed tumours arise in compound "cell-rests." With this theory is associated the name of Wilms,<sup>27</sup> who was the first to work it out fully for mixed tumours upon Cohnheim's lines. Wilms tells us that fibro-adenomata of the breast arise in germs of mammary tissue that were not used in the development of the breast. They remained in an undifferentiated, quiescent state until stimulated to growth by some external cause. As by then the natural relations with the surrounding tissues will have been grossly altered, their degree of differentiation is imperfect and their growth unlimited and blastomatous.\* Although tumours are therefore not necessarily or even generally congenital, they arise upon the basis of a congenital or developmental anomaly, a lack of differentiation with or without actual displacement.

I have pointed out in Study II. that Cohnheim's theory in this, its crude form, has been expanded to include all sorts of developmental anomalies. The essence of these hypotheses is that tumours are always referred to an *abnormal pre-disposition* and not to a perfectly natural or *physiological disposition* inherent in normal cells. The primary cause of tumour formation is sought in the presence of "tumour germs." Although external influences, such as irritation, etc., explain the growth in size of the germ, they are looked upon merely as secondary or liberating causes.

The next author I propose to mention who investigated these mammary tumours is Albrecht,<sup>1</sup> since he looked at them from an original and strictly scientific point of view. In his paper upon hamartomata he says :

It is the task of oncology not only to examine tumours, but also those structures that appear to be in any way related or similar to them, and thereby perhaps to establish on the one side a connection with other, normal or pathological formations, and so perhaps to initiate an understanding of certain kinds of tumours; and upon the other side perhaps to show that they are not to be included among tumours with certainty, if indeed they must not be separated from them.

\* Wilms' explanation of mammary fibro-adenomata with squamous epithelium (see Study VII.) is slightly more complicated. He assumes a cell-rest which consists of ectoderm and mesenchyme, displaced at an early period of development. Since mesenchyme is, however, derived in part from ectoderm, the germ may correspond with the latter alone. Wilms thus appears to have lost sight of the fact that the mammary epithelium is a downgrowth of the ectoderm. This is not so, however, since the explanation is to be found in his belief that the structure of every tissue is fixed and must retain its physiological type in all circumstances whatever.

The name that he applies to these tumour-like malformations is that of hamartoma, since they can be classed either as tumours or as tissue malformations, according to the point of view adopted by us. It will be well to let Albrecht speak for himself :

Even if, as I hope, you are in sympathy with the separation of the structures I have mentioned (cavernous angiomas of liver and spleen, fibromata of renal pyramids, tubular adenomata of liver) from tumours *sensu stricto*, I fear that this will no longer be the case with the following group. Nevertheless, it is possible to demonstrate that the peri-canalicular and intra-canalicular fibromata of the breast, at all events those specimens hitherto examined carefully by me, essentially belong to the same category.

This can be proved at once for the peri-canalicular fibromata, since it is easy to show that their tubules are branched according to the same pattern as the mammary acini, and that they differ from the natural acini only in the abnormal bulk of their connective-tissue sheaths and in the variation of their epithelium. But even in the case of the intra-canalicular fibromata that are so frequently combined with them it is possible in certain cases to show even macroscopically that the large slit-like channels that are often present unite after the manner of ducts into large branches, which not uncommonly contain milk in small quantities. Histologically it is often easy to demonstrate a form of tubular ramification which agrees more or less closely with the normal type. Occasionally I have been able to demonstrate areas in which the epithelium secreted milk. Although the development of the connective tissue is abnormally great, we must bear in mind that the type of structure of the organ is present in outline, and that the arrangement of the connective tissue corresponds with the course of the tubules.

Albrecht extends his arguments to tumours in general, and concludes :

We possess the sure indication that in a typical tumour the elements and more particularly the arrangement of the organ of origin are retained. In the light of this consideration the ætiological question is more particularly as follows : What are the causes that induce the error of development or, if we prefer it, the malformation of the tissues that ended in a tumour instead of a normal secreting lobule? The question of histogenesis is hereby included in the more comprehensive sphere of those of organogenesis or of the mechanism of development in the widest sense.

Albrecht was the first to point out clearly the close relationship of tumours and tissue malformations.\* Although he insisted in his writings<sup>2</sup> that nothing could be more wrong

\* See Study I., in which I have followed his views.



than to attempt to find a single causation for all tumours, and that many of them are no doubt the result of post-natal pathological processes, he believed that the hamartomata are produced by errors of development. These are due, in the case of mammary fibro-adenomata, to defective union or blending of tissues. Albrecht's advance upon Wilms' views appears to me to lie in the fact that he clearly realised that the primary cause of tumour formation depends upon and dates from an anomaly of blending. Although he assigned this anomaly to a period of life at which the tissues are undergoing differentiation, he showed the necessity for the action of a definite, tangible exciting cause, and emancipated himself from the concept of a primary abnormal pre-disposition of cells for tumour formation.

If we believe with Ribbert<sup>22</sup> that the growth of a tumour is always the result of intrinsic forces, it becomes impossible for us, however far back we trace it to its original beginnings, to imagine a time at which it was not autonomous and isolated in its mode of growth. We are forced, it seems to me, if we wish to be logical, to the conclusion Ribbert<sup>23</sup> himself ultimately drew,\* that all tumours must have been independent formations from the very beginning, represented as an anomaly of the very zygote itself, if not of the gametes that are joined to form it. The obvious association that exists between tumour formation and chronic inflammations, stages of involution, etc., like chronic mastitis, can only mean that the latter are secondary or liberating causes of tumour formation, which merely stimulate the anomaly or cell-rest, which was already present, to activity. Now this is, I am bound to assert, still the orthodox view held by the majority of pathologists to the present day, simply because they will not think out Cohnheim's theory to its logical conclusion. How otherwise can we interpret, for instance, the explanation of the ætiology of mammary fibro-adenomata given by Ewing,<sup>6</sup> in the largest and most comprehensive textbook on tumours in the English language?

I find as a rule that tumour-like areas in chronic mastitis are not well circumscribed and show many inflammatory changes, such as the growth of fine capillaries and infiltration with round cells, while the pronounced tumours are free from inflammatory signs. It seems probable that an inflammatory process is a frequent inciting factor especially with the cyst-adenomas, but that a true tumour arises only when there is a predisposition in the form of superfluous or misplaced material. A constitutional element may also be assumed.

\* Ribbert's constant shifting of his position appears to me to be natural and the outcome of logical necessity.

The time has assuredly come for pathologists to realise that a species is nothing more than a concept. However useful it may be in systematics it does not exist in nature, except as an accident, until the time when evolution will have ceased. Let us get away from the methods of simple description, and even of naïve realism if need be, and try to employ those of science instead. We are not in want of an example to guide us, since Albrecht, in setting up the far-reaching and truly scientific category of the hamartomata, has shown us twenty years ago that there is no distinction between "true" and other species of tumours.

We will not stray into the quicksands of ætiology, a course I have hitherto tried to avoid as far as possible in these studies in histiogenesis, and return to earth which, though boggy, is moderately safe. We will adopt the methods suggested by Albrecht,<sup>1</sup> and compare the fibro-adenomata of the breast with the hyperplastic lesions of chronic mastitis. The association of these conditions is so widely known that we need not waste time in pointing it out. We must, however, bear in mind, remembering what we have said above and that questions of ætiology are closely connected with those of histiogenesis, that the association is either primary or secondary. If it be of the latter kind we shall fail to find evidence pointing to a gradual transition from hyperplastic nodules to those we are justified in calling fibro-adenomata. If, however, the association be primary, we should find indications at least that the double parenchyma of our tumours is derived from the epithelium and the stroma of the mammary gland.

Although the close association of fibro-adenomata with chronic mastitis is referred to in most of the papers upon the pathology of the breast, comparatively little systematic histological work has been carried out upon it. Most of the literature deals primarily with the clinically far more important malignant tumours, and fibro-adenomata are treated more or less as a side issue. Our purpose will have been served with the mention of two papers only.

Theile<sup>25</sup> examined twenty-one cases of chronic mastitis with or without a coincident malignant neoplasm. He demonstrates the impossibility of separating the fibro-adenomata as tumours from the hyperplastic nodules to be seen in chronic cystic mastitis. Limitation within a circumscribed area and capsule formation are the only criteria by which we can recognise a tumour. All the changes that lead to fibro-adenomata are present in the diffuse forms of mastitis. Nature does not confine herself within sharply defined categories. Fibro-

adenomata, cyst-adenomata and chronic mastitis together form a single group. They arise in identical primary histological changes, that differ among themselves solely by their greater or lesser degree of isolation, and by the preponderance and greater activity of the connective tissue in one case and of the epithelium in another.

Cheatle<sup>4</sup> points out that the position of the peri-epithelial elastic layer varies in different forms of hyperplasia of the connective tissue in cases of chronic mastitis. These differences are maintained in fibro-adenomata of the peri- and intra-canalicular types (*v. supra*). He emphasises the fact that all stages of diffuse and nodular hyperplasia and definite tumour formation are to be found in the same breast, around the ducts as well as the acini. In speaking of the diffuse form of *hyperplasia intra-elastica* he says that localised tumours may arise from it. This form of hyperplasia

concerns the fibrous tissue immediately outside the ducts, and the intra-lobular connective tissue of the acini, and includes mainly well-known varieties of fibro-adenoma of the breast.

In describing a peri-canalicular fibro-adenoma of this class he makes the following statements :

It is important to observe that the tumour increases in size in two ways : first, by hyperplasia of the epithelial and fibrous tissue in the original tumour formation, and secondly, by an exactly similar affection recurring in fresh areas of the breast. The newly affected areas may be in juxta-position to the original tumour, or they may be separated from it by comparatively normal breast-tissue; then serial sections show that the fresh area may be quite separate from the original tumour, although it may be forming in part of the same segment of the breast. The importance of this observation lies in the inevitable conclusion that this so-called fibro-adenoma is really a process affecting consecutive parts in a localised area of a gland that has been normal.

A diffused form of extra-elastica hyperplasia of fibrous tissue may occur in a peri-canalicular and peri-acinous form, and may affect practically the whole of the breast. Among this diffused condition can be seen an occasional small isolated tumour which exactly resembles a peri-acinous and pericanalicular fibro-adenoma.

The occasional overlapping of one class (of hyperplasia of the connective tissue) by another occurs so definitely that the trend of my observations is as follows : All the pathological changes to which I have drawn attention (and I include carcinoma) may be phases of a consecutive evolution of disease.

Cheatle's statements are fully borne out by his excellent figures, of which I would particularly draw attention to Fig. 367. It shows a small fibro-adenoma almost completely surrounded by a capsule formed of the inter-lobular or supporting fibrous tissue of the breast. It blends, upon the left side of the drawing, with almost normal mammary lobules, in one of which the inter- and peri-canalicular changes of the intra-lobular connective tissue characteristic of the tumour are beginning.

My material is not a first-class one for the elucidation of the question of the identity or disparity of the changes of chronic mastitis and the fibro-adenomata, since it was obtained exclu-

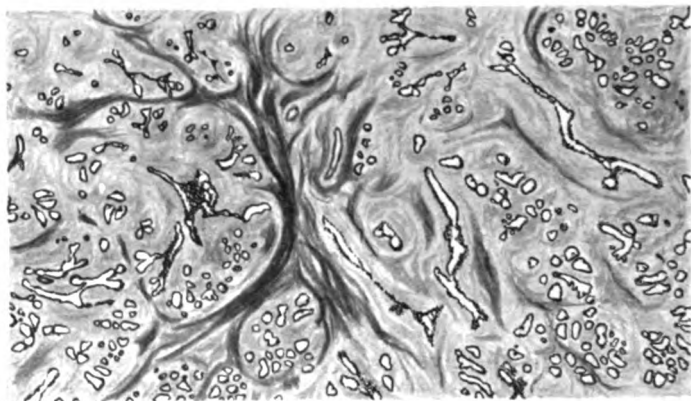


Fig. 79.

Centre of fibro-adenoma of breast with structure of mammary gland.  
Magnif., 25.

sively by operation. There is usually very little mammary tissue present around the isolated encapsulated tumours. Nor have I prepared sections of whole breasts as Cheatle has done. I have therefore not examined thoroughly the general changes in the tissues of the breast that are associated with fibro-adenomata. Nevertheless, study of the tissues at the circumference of these tumours and a comparison of their structure with that of cases of chronic mastitis has enabled me to form opinions concerning the histiogenesis of the fibro-adenomata. These have been strengthened by my good fortune in having had opportunities to examine many of Sir G. Lenthal Cheatle's specimens.

Fig. 79 is a low-power drawing of part of a large encapsulated peri-canalicular fibro-adenoma. It shows many slightly dilated intra-lobular ducts, into which there open groups of acini,

imperfectly separated off into lobules. The general connective-tissue parenchyma of the tumour is loose and possesses the oedematous-looking, often called myxomatous, structure characteristic of the intra-lobular stroma of the breast. It forms more or less evident sheaths around the acini and lobules. They become indistinct and fused with each other between the lobules. Irregular strands of dense fibrous tissue are present around some of these. They have the structure and the capacity to be stained deeply with eosin of the inter-lobular or supporting fibrous tissue of the breast.

I have reproduced this drawing here, since it demonstrates more clearly than pages of description the general structure and architectural plan of a fibro-adenoma mammæ. These correspond exactly in essentials with those of the normal breast. They differ merely in detail: In the distortion of the epithelial tubules; in the excess of the loose intra-lobular connective tissue; in the diminution of the supporting dense fibrous tissue; and in the complete absence of adipose tissue.\* Had the latter been present I would defy any man to differentiate the central fields of this tumour from chronic mastitis. Looked at from an anatomical standpoint, this fibro-adenoma has all the characters of a tumour and of a tissue malformation. It is a hamartoma in accordance with Albrecht's<sup>1</sup> definition.

The specimen is far from unique. Almost every peri- and intra-canalicular fibro-adenoma in my collection would have been equally suitable to establish the conclusion I have drawn. A glance at Fig. 8 (I.) is sufficient to prove this.

A question of great importance for the correct appreciation of the morphological and oncological status of mammary fibro-adenomata, as well as for their histiogenesis in general is this: How does a fibro-adenoma grow? There can be no doubt that it grows in two ways. In perhaps 99 per cent. of cases (although I believe this percentage to be much too high) the growth of an established fibro-adenoma is always closed, or independent of its surroundings. In this respect it conforms with Ribbert's<sup>22</sup> law. But in a few cases the histological evidence is quite conclusive that it increases in size by appositional growth as well. The surrounding mammary lobules undergo the same minute changes that have already taken place within the body of the tumour, and are absorbed or incorporated into its substance. Cheate<sup>4</sup> has already drawn this conclusion. I regard his statements as of the greatest value, since he is

\* I used to be taught as a student that the best way to tell a fibro-adenoma from chronic mastitis is by the absence of adipose tissue in the former. I am not sure even yet that it is not the only way.

primarily a surgeon untrammelled by current pathological doctrines, who is free to describe what he has actually seen, and not what he ought to have seen. He has worked with serial sections, so that every doubt concerning his facts is removed. I, for one, agree fully with his interpretation of these facts.

I have examined serial sections of a part of the periphery of the tumour illustrated in Fig. 80. I have thus been able to trace a few of the smaller nodules in question and have found that they are completely isolated. This tumour is an intra-

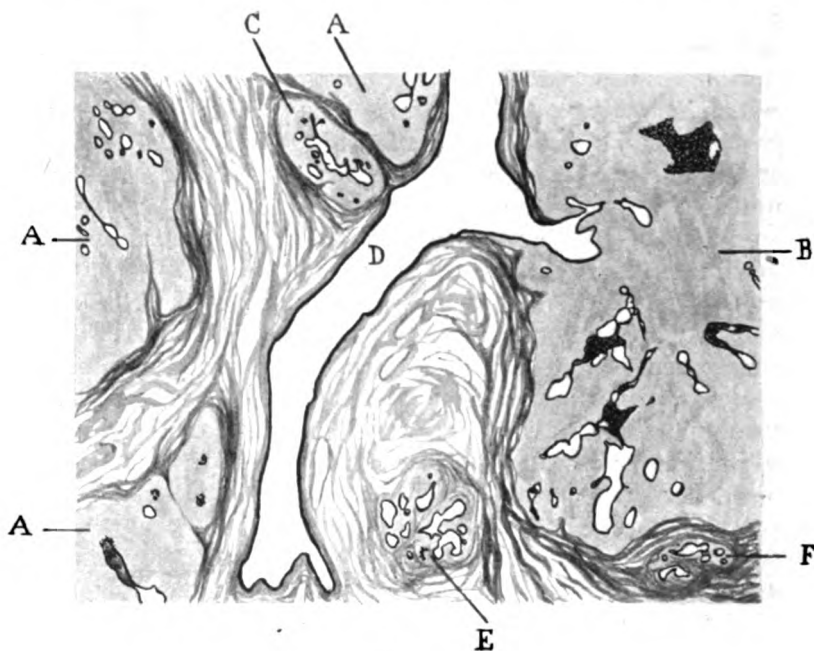


Fig. 80.

Mammary fibro-adenoma with appositional growth. Magnif., 20.

canalicular fibro-adenoma which measured nearly 2 cm. in its greatest diameter. It was well defined with the naked eye and surrounded by a capsule, out of which it could be easily shelled at the place where I tried to do so. Its surface was nodular, and some of the nodules were torn away by this manipulation. The surrounding mammary tissue presented a somewhat irregular, "lumpy" feel. The tumour was excised from a woman of 51 with a mild degree of generalised chronic mastitis of both breasts.

The microscope shows that the tumour is surrounded by a rather loose fibrous capsule, which represents the condensed

supporting tissue of the breast, in which the remains of acini and ducts have persisted. It gradually fades into the general inter-lobular fibrous tissue. The capsule sends coarse, broad septa into the substance of the tumour, some of which gradually disappear near its centre, whereas others are complete and divide... it into well-defined lobes. Narrower secondary septa are given off, which again are complete or incomplete. Where these septa are very broad they contain more or less unaltered inter-lobular fibrous tissue as well as adipose tissue. The nodules included by them are sometimes completely isolated. The larger of these are surrounded by a capsule of their own, formed, as in the main tumour, by condensation of the supporting inter-lobular fibrous tissue. Part of one of these nodules is shown at B in Fig. 80. The body of the tumour is represented at A, A as the ends of three lobules, all of which are definitely incorporated in it. The general supporting stroma of the breast occupies the intervening space. It is condensed around the circumference of A and B into definite capsules. It sends two broad septa into the tumour, both of which eventually disappear near its centre. C is a small nodule with a well-defined capsule. The structure of its parenchyma is identical with that of A. It is completely isolated except that it communicates at a different level of the series with the large duct D. This communicates in a similar manner with the tubules of B and has given off a branch near the lower border of the drawing, which can be traced to the nodule E. The latter exhibits all the changes seen in A, B and C, but in a smaller degree. It is not surrounded by a definite capsule and is invaded by the general supporting stroma of the breast near its lower pole. F represents a small isolated mammary lobule whose epithelial tubules are slightly dilated and proliferated. D passes out of the series at either end.

E and F are mammary lobules. This is proved by comparing their structure with that of other lobules in the specimen situated at greater distances from the fibro-adenoma, as well as by the fact that E communicates with duct D at a different level than the one represented in the drawing. They are lobules whose tubules are dilated and show evidence of a slight degree of proliferation, and whose intra-lobular stroma is hyperplastic. This change has led, in the case of E, to a certain appearance of isolation as well as to a slight amount of enlargement. The latter has, however, remained within physiological limits, and is only appreciable by the fact that the fibrous tissue around the greater part of its circumference has a concentrically laminated structure, which is responsible for the appearance of isolation described above, and must have been produced by the

pressure of the growing lobule. C is, however, completely encapsulated. Its connective tissue is greatly in excess of the epithelium. Its structure is very similar to that of E, *i. e.* of a mammary lobule. C can thus be explained as a lobule whose stroma has undergone hyperplasia, in which the epithelium has participated to a smaller extent. The lobule has grown in bulk because of this proliferation. It has exerted an ever-increasing amount of pressure upon its envelope of supporting fibrous tissue. This has responded by compression and sclerosis and has produced the capsule of C. These processes may be taken to have obliterated the capillaries that may have extended into C from the neighbouring inter-lobular fibrous tissue (*v. supra*, the reference to Ewing<sup>6</sup>). C has thus become an isolated encapsulated nodule, still, however, connected with its duct and supplied with blood by one or at most a very few nutrient vessels. Were it to have increased in size at a later date, it could only have done so by growth of its own tissues. It has acquired the characters of an independent encapsulated fibro-adenoma; it is a hamartoma in the terms of Albrecht's<sup>1</sup> definition.

I need say little about the minuter structure of these nodules and lobes, since I have nothing to add to the excellent descriptions of Theile<sup>25</sup> and Cheate.<sup>4</sup> Suffice it to say that they exhibit all stages of proliferation of epithelium and intra-lobular connective tissue between the recent and early changes seen in E and the fully developed peri-canalicular fibro-adenoma in C, B and A. At one end of the series of sections, where B is much smaller and the general mammary stroma between it and duct D consequently much looser, there are present several normal mammary lobules, one of which is continuous with E, whose other end it represents.

I conclude that B and C, although they are independent encapsulated peri-canalicular fibro-adenomata in accordance with oncological nomenclature, are nevertheless morphologically hyperplastic mammary lobules.

Since the tumour in question had been growing steadily in size, there is no reason to suppose that it would not have continued to do so had it not been removed. What are we reasonably to assume to have happened in this case? E would have grown, its structure would have come to resemble that of C more and more closely, and it would have become completely isolated from the surrounding fibrous stroma, which would have formed a capsule for it. C would have increased steadily in size by expansive growth of its tissues. Nor can we doubt that B and A would have done the same. The nodules would



therefore have approached each other more and more closely. At the same time they would have encroached upon the general fibrous tissue of the breast, which would be reduced to dense capsules around them, and would later assume the appearance of fibrous septa between the expanding nodules. At a still later stage the septa would undergo atrophy because of the ever-increasing pressure of the growing nodules. The parenchyma of these would now come into contact and fuse. Incomplete lobules in a single tumour would result. The structure of the oldest central parts of our fibro-adenoma indicates clearly that this is what has actually happened here. Long before the changes we have assumed could have taken place duct D would have been obliterated, E would have grown to a large size and would soon have fused with A, B and C. More distant mammary lobules may even be assumed eventually to have participated in these changes.

Ribbert's <sup>22</sup> law of the closed, independent growth of all tumours therefore does not apply universally. I could instance several other mammary fibro-adenomata I have examined as exceptions to it, since they show the same evidence of appositional growth as the one I have selected. Fig. 8 (I.) suggests that the septa of fibrous tissue separating the lobules from one another have arisen in this way, and so does Fig. 79. I believe that this is often the true explanation.

These arguments can be briefly summarised thus : In addition to closed expansive growth of the cells of their parenchyma, fibro-adenomata of the breast sometimes exhibit evidence of appositional growth brought about by the successive implication of neighbouring mammary lobules, which may open into the same duct. Their tissues undergo hyperplasia. This does not differ histologically from that seen in distant lobules of the same breast in cases of chronic mastitis (Cheate <sup>4</sup>). The hyperplastic lobules are soon isolated by local condensations around them of the supporting fibrous stroma of the breast in the form of capsules. Their growth hereby becomes independent and expansive. The lobules eventually fuse to form a single fibro-adenoma because of pressure atrophy of their capsules.

I draw the same conclusions as Theile <sup>25</sup> and Cheate <sup>4</sup> : There are no essential differences, but only differences of degree between fibro-adenomata of the breast and the hyperplastic changes of chronic mastitis. Like my predecessors I have traced every degree of hyperplasia between histologically normal mammary lobules and fibro-adenomata.

What light does the structure of the tumours throw upon their histiogenesis? Need we assume the presence of a cell-

rest or other congenital abnormal predisposition, or can we dispense with these?

The fact that we have traced an uninterrupted series of changes, with normal mammary lobules at one end and fibro-adenomata at the other, renders the assumption of undifferentiated cell rests unnecessary. Firstly, we should have to assume their presence in large numbers in cases like the one illustrated in Fig. 80. This would be difficult, although by no means impossible. Secondly, and this is very much more to the purpose, we should have to assume that these cell-rests develop into structures that are histologically indistinguishable from the physiological lobules of the breast before they proceed to tumour formation. We cannot tolerate this assumption for a moment, since it spells madness. If a cell-rest, destined to become a tumour can, on the way, assume structural identity with a normal organ all knowledge of morphology and physiology tumbles in ruins at our feet.\*

The assumption of an abnormal congenital pre-disposition, in its widest sense even, is equally unnecessary and gives rise to the same kind of difficulties. Were we to assume that the apparently normal lobules undergo tumour formation because they are "delicate," † what is to hinder our neighbour from turning round our assumption and maintaining that the only way in which they display their delicacy is by undergoing tumour formation? We gain nothing by this pseudo-explanation.

I protest most vigorously against the use of the phrase "constitutional element" in tumour formation. Translated into plain English it means neither more nor less than: "A factor which we do not understand and have no desire to investigate." The assumption of a constitutional factor is no doubt highly proper in clinical medicine, but it should have no place in pathology, whose duty and pleasure it is to investigate all the unknown factors in disease.

It is the aim of a scientific explanation or formula to subsume the facts it has been formulated to deal with under as few and as simple concepts as possible, provided they be applicable to all the facts subsumed. It is therefore the essence of a scientific theory to omit all unnecessary concepts, especially if these be hypothetical or unsupported by adequate evidence, and to replace them by others based on known facts. Should the

\* The third argument against cell-rests forms one of the principal theses of these studies and need not be repeated here.

† We have good morphological and physiological evidence in the case of a delicate child, but I know of none pathognomonic of delicate cells or tissues.

theory itself tumble to pieces during this cleansing process, so much the better for us.

I believe that the following facts have been established by Theile,<sup>25</sup> by Cheate,<sup>4</sup> and in the present paper :

1. An uninterrupted series of changes has been traced between the structure of normal mammary acini, of cases of chronic mastitis, and of unimpeachable fibro-adenomata of the breast.

2. Appositional growth has been shown to occur in fibro-adenomata.

3. The gradual isolation of mammary lobules and the assumption of an independent, closed mode of growth by them is the result of the formation of a capsule around them and of the gradual expansion of the lobule within this capsule.

I admit that these facts do not definitely disprove the theory that fibro-adenomata of the breast are the result of a congenital predisposition, provided it be assumed that this be sufficiently widespread in the tissues of the breast. It is the strength of or, as I prefer to think, the weakness of a theory like that of Cohnheim and its later modifications that it can no more be disproved than it can be proved. We must be satisfied if we have shown that it is both unnecessary and illogical.

But the observed facts appear to me to indicate a diametrically opposite view since, if I read them aright, they point to the conclusion that every lobule of the breast, far from having to be abnormally pre-disposed for tumour formation, is physiologically disposed or, to use the language employed in embryology, possesses the potency to give rise to a fibro-adenoma. I therefore regard tumour formation, in so far as it concerns the mammary gland and the tumours under consideration, as a perfectly normal or physiological process which must inevitably take place in every mammary lobule in certain circumstances. I thus find the incentive, or the exciting cause of tumour formation not in an abnormality of the cells of the breast, but in a reaction to a set of abnormal conditions present in chronic mastitis, in a physiological reaction to an abnormal environment.

I thus find myself in disagreement with Albrecht,<sup>1</sup> who believed that these tumours originate in congenital malformations. I have pointed out in Study II., where I described two very early fibro-adenomata of the breast (Figs. 35 and 36), that I would extend the term "malformation" to include the disturbances set up in the tissues by pathological lesions in adult life. Fundamentally, however, I am in agreement with Albrecht, since he had as little use for a *vitium primæ formationis* in tumour formation as I have.

The view I advocate appears to me to possess certain advantages over theories based upon the assumption of abnormal predispositions. It allows that the processes of the body are orderly, natural and physiological in the true sense of the word. They are the inevitable and only possible response to the environment (see VII., p. 844). As long as the latter remains normal they will be so too, but when it becomes altered or abnormal, the reactions will alter and become pathological to a corresponding extent.

By adopting this view we correlate and subsume the histological changes to be seen and inferred in the development and growth of mammary fibro-adenomata under strictly biological or physiological categories. No process has been found in the cells of these tumours that is not present in normal development and growth. I do not wish to generalise, but it seems to me that the cause of tumour formation can in these cases be definitely removed from the cells of the tumour and relegated to pathological processes external to them. In the words of Albrecht : <sup>1</sup> " The question of histiogenesis is hereby included in the more comprehensive sphere of those of organogenesis or of the mechanism of development (and, we may add, growth) in the widest sense." \*

### Conclusions

1. The view that fibro-adenomata of the breast are the result of an abnormal pre-disposition of the cells in which they have arisen is unnecessary and illogical.

2. There is evidence to show that it is one of the potencies of every physiological lobule of the breast to give rise to a fibro-adenoma.

3. The primary or exciting cause of tumour formation is thus not to be sought in an anomaly of the cells of the breast, but in an abnormality of their environment.

### APPENDIX

*Heterotopic Tumours of the Vagina and Bladder.*—Wilms <sup>27</sup> collected certain rare tumours of the vagina and of the fundus of the bladder. They are characterised by the presence of a cambium layer of cells that undergo differentiation into cartilage or striped muscle, in addition to derivatives of the mesenchymal constituents of these organs. Although these tumours usually

\* I see no difficulty in the possible presence of mammary fibro-adenomata at or soon after birth, since I hold that identical processes are at work in the embryo and the adult.

contain either cartilage or striated muscle only,\* he included them with the mixed tumours, since he argued that they have originated in displaced mesodermal cell-rests, in which differentiation proceeded in one direction only, either that of the cells of the sclerotome or of the myotome. Since the Wolffian duct is closely related with the base of the bladder in the male, and he knew of no instances of an analogous vesical tumour in the opposite sex, and since the corresponding new growths of the vagina are usually found in its anterior wall, close to the lower end of Gärtner's duct, Wilms argued that the displaced cell-rest is carried by the Wolffian duct in both sexes. He admitted that the cell-rest might be carried by Mueller's duct, but did not discuss this alternative mode of transport, with the intention, no doubt, of establishing a single origin for all these urogenital tumours.

In the fact that the "germ" of these tumours is apparently transported exclusively by the Wolffian duct, Wilms and his successors saw a strong piece of evidence in favour of Cohnheim's theory. They were compelled to assume the presence of a "rest" composed of undifferentiated cells, whose development has persisted at the stage of the primitive mesoblast, because they refused to admit that it is possible for heterotopic tissues to arise by differentiation of the cells of the part in an unusual direction. They quite rightly insisted that this does not happen in a normal individual. But are the potencies of cells limited by their fate in the normal organism, or are they greater? I believe that the latter is the case, upon good and sufficient evidence, I trust (see <sup>21</sup>, as well as earlier studies). I can see no reason why a tumour containing cartilage (*cf.* Fig. 78) or even striated muscle should not occasionally arise in the mesenchymal tissue cells of the bladder or cervix.

But what does Wilms' evidence amount to? I. Since the trigone of the bladder and the ureters have the same developmental history in both sexes, being the representatives of the fused Wolffian ducts and their ureteric buds, what is to prevent these structures from containing undifferentiated mesoderm cells in the female if they are present in the male? II. These mixed tumours have since been found in the fundus of the bladder in the female sex, *e. g.* by Moenckeberg,<sup>16</sup> who saw a rhabdomyoma in a young woman of 28. III. Identical mixed tumours arise in the fundus of the uterus, which does not enter into close relationship with the Wolffian duct in development. I need but mention the cases of Glynn and Bell,<sup>8</sup> who give an excellent

\* Beneke's <sup>3</sup> tumour of the bladder, in a man of 72, contained hyaline cartilage, osteoid tissue and striated muscle.

résumé of the literature, that of Murray and Littler,<sup>17</sup> as well as the case described by me.<sup>20</sup> IV. Fibres of skeletal muscle were observed in the uterine wall after delivery by Nehr Korn<sup>18</sup> and in that of the bladder of a pregnant woman by Hofbauer.<sup>10</sup> V. We should bear Meyer's<sup>15</sup> warning in mind that it is a mechanical impossibility for the Wolffian duct to carry away cells during the period of its caudad growth. Lastly, all the evidence we possess of the persistence of embryonic cell rests in an undifferentiated state *in situ* is represented by Fischer's<sup>7</sup> nodules of renal blastema in a boy of 8 and a youth of 16. No one has yet described an undifferentiated *displaced* cell-rest.\*

It appears to me that the evidence in favour of Cohnheim's theory and its modifications, when critically examined, is as slender in the case of Wilms' mixed tumours of the bladder and vagina as elsewhere.

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\* Meyer<sup>14</sup> records the presence of two spicules of immature bone surrounded by osteoblasts in the lateral part of the cervix uteri of a four months' fœtus, just above Gärtner's duct. He admits that it is not an indifferent meso-dermal cell-rest, but a moderately well-differentiated germ of the sclerotome, which was undergoing physiological differentiation and not tumour formation. He argues that its close connection with the remnants of the Wolffian duct indicates that it had actually been carried by it. But it seems to me that the possibility of its being an instance of heterotopic inflammatory bone formation on the basis of a calcified necrotic focus cannot be excluded, in spite of the fact that there were no signs of inflammation or calcification. Be this as it may, the significant fact remains that it had undergone a high degree of differentiation in a fœtus of the fourth month.

## A CASE OF TEMPORO-SPHENOIDAL ABSCESS, SECONDARY TO ACUTE OTITIS MEDIA

By E. HORACE RICHARDS, M.B., from the Ear and Throat Department,  
Guy's Hospital.

MOST authorities consider that brain abscess is more frequently the result of chronic than of acute otitis media, though some American writers state that acute otitis accounts for as many as, if not more than, chronic otitis. However this may be, all agree that some disease is almost invariably present in the middle ear, antrum or mastoid cells at the time when the abscess is diagnosed.<sup>1</sup>

A fairly thorough search through recent literature revealed a number of cases of brain abscess as a sequel of acute otitis media, but no case was found in which it was definitely stated that the otitis had cleared up or that the antrum showed no macroscopical change.<sup>2</sup> It may therefore be concluded that the following case is one of considerable rarity and interest.

H. W., a youth aged sixteen, attended in the Aural Department in May 1928 on account of earache on the left side. Seven years previously he had had right-sided otitis, for which a simple mastoid operation had been performed with complete success: on this side the membrane was normal and the hearing also.

The left ear showed acute otitis with bulging drum; this was incised and pus escaped; under appropriate treatment the otorrhœa ceased in about fourteen days, and all local symptoms and signs disappeared.

Some days later the boy complained of headaches; as no local condition was found to explain these headaches the patient was transferred to the care of Dr. C. P. Symonds. He was subsequently admitted under Mr. W. M. Mollison on the advice of Dr. Symonds.

On admission on July 22 he looked very ill and was complaining of severe headache. The headache was frontal, mostly left-sided, throbbing and continuous, definitely worse at night, and with occasional exacerbations, during which the pain was of such severity as to make the boy groan and shout incoherently. He often had vertigo with sensation of rotation of surrounding objects to the right. He frequently vomited, but without nausea, sometimes after food and sometimes on getting out of bed. He suffered from insomnia at night, but

during the day from increasing drowsiness and a tendency to fall asleep if left undisturbed.

There was no history of chills or rigors. He had been losing weight. Usually a placid, happy boy, he had lately become very irritable and resentful, noises especially distressing him. He had given up all reading and for three weeks had complained of pain and defective vision in the left eye with diplopia on looking to the extreme left. At school he had reached Standard 7, but recently, when copying a letter, had substituted many wrong words and unknowingly had altogether omitted several others, but at the same time his writing had been good; these faults were apparently in no way due to carelessness.

His parents remarked that for some time he had frequently misnamed ordinary objects and occasionally found himself unable to make himself understood on account of this inability to recall the necessary names; especially was this peculiarity noticeable at meal-times, when he would ask for "some more of that!" being quite unable to find the required word, but instantly able to recognise the correct name of the dish required, if suggested to him. Then he would be able to recall the word spontaneously for some time afterwards.

This aphasic condition was made evident by an examination of the patient's ability to name each of twenty-four objects selected at random. He failed to name five only, but could easily describe their usual uses, and was at once able to recognise their names from a series of words suggested, and when shown these five objects again later, was found capable of naming them instantly, correctly and without hesitation.

He had a slightly subnormal temperature, and the pulse rate varied between 80 and 90.

The central nervous system alone presented pathological features, the following signs being observed:

(1) Slight asymmetry of the lower part of the face with slight apparent weakness on the right side.

(2) Nystagmus, combined horizontal and rotatory, spontaneous to both sides, but more marked on looking to the left with the quick movement in the direction of vision, unaccompanied by vertigo.

(3) Diplopia, the images corresponding to paresis of the left external rectus and inferior rectus muscles.

(4) Feeble abdominal reflexes limited to the left lower quadrant of the abdomen.

(5) Bilateral papilloedema to the extent of six diopters.

(6) Sensory aphasia.

A leucocyte count showed a polymorphonuclear leucocytosis of 10,150 per cub. mm.

Otological examination revealed a dry cavity and healed membrane on the right, and on the left absence of pain or tenderness to pressure and percussion, a dry meatus and a normal membrane with slight injection of vessels along the handle of the malleus.



Hearing on both sides was good and equal with normal relation between conduction by air and bone.

The vestibular reaction to syringing with cold water was well marked, vomiting being easily produced on testing the right side, and marked nausea on the left: nystagmus was normal and accompanied by apparent rotation of surrounding objects towards the side tested.

From these symptoms and signs an abscess in the left temporo-sphenoidal lobe was diagnosed, the symptom of sensory aphasia being considered to be almost pathognomonic. The left mastoid was opened. The bone was found to be normal; the antrum and the dura mater of the lateral sinus were macroscopically normal, but the dura of the middle fossa, though normal in colour, was seen to be slightly bulging.

The dura mater of the middle fossa was widely exposed, painted with liquefied carbolic acid and incised in a crucial manner. The cerebral cortex, covered by healthy-looking pia-arachnoid, then slightly prolapsed. On exploring the posterior part of the second temporal convolution with sinus forceps, a definite tense capsule was appreciated about one inch from the surface of the brain; about an ounce of thick, creamy, non-odorous pus was evacuated on piercing this capsule.

The opening into the abscess was enlarged by separating the blades of the forceps and a tracheotomy tube was inserted into the abscess cavity: dry absorbent dressings were applied, but no sutures were used.

The pus evacuated produced a pure culture of long-chained *Streptococcus longus*. Swabs from the mastoid antrum and the extradural space gave no growth after seventy-two hours' incubation at 37° C.

Twenty hours after the operation, no pus was found to be draining viâ the tube, nor was there any herniation of cerebral tissue. The tube was then removed, and no further drainage of the abscess cavity was carried out.

The pulse rate remained between 80 and 90, and there was complete absence of headache.

The wound was allowed to heal gradually by granulation, and during the following ten days sleep at night was undisturbed, the diplopia diminished, the papilloedema decreased to four diopters, and there was a general feeling of well-being.

On the eleventh day, frontal headache recurred, but was not of sufficient intensity to interfere with sleep; it persisted for ten days and then finally disappeared.

Diplopia was absent after the fourteenth day.

Aphasia disappeared at the end of three weeks, but the papilloedema remained constant at about one diopter.

The spontaneous nystagmus disappeared after four weeks, when the boy, feeling and looking in the best of health, was allowed out of bed for the first time.

There has been no recurrence of symptoms up to twelve

weeks after operation. Hearing, tested at the end of September, was found normal.

It seems quite clear that the cerebrum was indirectly infected from an acute otitis media, which had completely resolved under local treatment within a short space of time.

Subsequently an abscess formed in the left temporo-sphenoidal lobe, the diagnosis and localisation of which rested almost entirely on the recognition of one symptom—sensory aphasia, of such a slight degree that a casual examination might well have resulted in failure to demonstrate its presence.

No sign of disease or infection was found in the temporal bone, and yet an encapsulated abscess was discovered on exploring the posterior third of the second temporal gyrus, and a considerable amount of pus, giving a pure culture of streptococci, was evacuated.

Neumann,<sup>8</sup> after an extensive study of brain abscess, came to the conclusion that diplococci, and streptococci to a lesser degree, have a characteristic property in their ability to produce “an abundant secretion of fibrin from the blood of the brain substance immediately surrounding an inflammatory centre, which eventually results in the separation of the abscess cavity from the surrounding tissue by a firm and tough fibrinous capsule.” So convinced is he of this characteristic, that he regards the demonstration of these organisms in pure culture as “strong inferential proof of the existence of a well-defined abscess capsule.”<sup>4</sup>

Upon considerations such as these, the limitation of the drainage of the abscess cavity to such time as the flow of pus had ceased, and the tendency to herniation had disappeared, was undertaken.

The Schwartze operation provided ample exposure for the exploration of the posterior third of the temporal lobe, while conserving the tympanic structures and not impairing their function.

The recognised routes for the spread of infection from an otitis media into the substance of the brain are three :

(a) “directly from a collection of pus in relation to an erosion of the tegmen tympani or antri”; the abscess then is “invariably in continuity with the original focus of infection across an area of meningeal adhesion”;<sup>3</sup>

(b) indirectly viâ venous channels;

(c) along perivascular lymphatic spaces, apparently unaltered tissue intervening.<sup>2</sup>

Ballance states that infection may be carried by the blood

stream and cause suppuration in the brain "at a considerable distance from and without obvious connection with the primary focus in the bone."<sup>5</sup>

MacEwen, writing in 1893,<sup>7</sup> asks, "Can an abscess form in the brain from infective otitis media purulenta and remain *in situ* while the middle ear disease becomes cured?—Such a condition is highly improbable . . ." is his reply. He then quotes a case under Gruber, in which a man had had acute otitis and acute mastoiditis, which was cured at the end of six weeks; three months later he died and at post-mortem examination an abscess with a definite capsule was discovered in the right temporal lobe, while no abnormality was found in the temporal bone except some thickening of the tympanic membrane.

This case answers MacEwen's question in the affirmative.

I am indebted to Mr. W. M. Mollison for permission to publish this case and for his help in the preparation of this paper, and to Dr. C. P. Symonds for help in the investigation of the nervous system.

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# A NEW OPERATION FOR OZÆNA

By N. E. KENDALL, F.R.C.S.E.

(From the Ear and Throat Department)

OPERATIONS for the treatment of ozæna may be divided into three groups.

- (a) Those that aim at keeping the nasal mucous membrane moist by means of saliva; an example of this is Wittmaack's<sup>1</sup> operation for implanting Stenson's duct into the antrum.
- (b) Those that aim at attacking the nasal sinuses and narrowing the nasal chambers; *e.g.* Lautenschläger's<sup>2</sup> operation.
- (c) Those that aim at narrowing the nasal chambers, and only deal with the sinuses if found to be infected.

The operations about to be described belong to the third of these groups, but are only attempted after all sinus infection has been treated or proved to be absent. The technique differs only slightly from the routine operation for resection of the septum. For these new operations is claimed a simplicity which is not found in other operations of this group.

The first of these suggested operations is reserved for those cases in which there is unilateral ozæna with a marked convexity of the cartilaginous septum towards the unaffected side.

The second operation is adapted to cases of bilateral ozæna, and for those in which the disease is unilateral, but unassociated with any lateral deviation of the septal cartilage.

## 1. OPERATION FOR UNILATERAL OZÆNA

In these cases there is a very marked deviation of the septum which obstructs one side of the nose and leaves the other side very roomy. On the roomy side there are the crusting and factor typical of ozæna.

An incision is made on the convexity of the septum in the usual way, as for submucous resection, the muco-perichondrium is carefully raised, and part of the cartilage is removed by means of a Ballenger's swivel knife, care being taken to leave some cartilage above and below; the amount left should under

no circumstances be less than a quarter of an inch in depth. The cartilage removed is next trimmed and reinserted with its long axis in a vertical direction and the convex surface reversed, so that it now faces the affected side and its upper and lower margins are wedged, also on the affected side, against the cut portions of the septum previously left for the purpose.

The mucous membrane is replaced in position, and the nose on that side is lightly plugged for twelve hours.

The result of this procedure is that the previously spacious side of the nose is diminished by a reversal of the cartilage removed.

## 2. OPERATION FOR BILATERAL OZÆNA, AND THOSE CASES WITH NO LATERAL DEVIATION OF THE SEPTAL CARTILAGE

In this operation there is no removal of cartilage, since this would in no way diminish the extent of the nasal fossæ.

Cartilage, on the other hand, is added to the septum on both sides, and it may be convenient to obtain the necessary tissue from the patient himself or from another patient.

In the first case a piece of costal cartilage is removed, but, in the second case, the septal cartilage removed from another patient at a previous operation is utilised.

Whatever the source selected, the cartilage is divided into strips of appropriate length and inserted between the muco-perichondrium and the cartilage of the patient by means of an incision similar to that already described.

It will be found necessary at a later date to perform a similar operation upon the other side of the nose. It is not advocated that both sides be dealt with simultaneously.

In all cases it is advisable, previous to operation, that care should be taken to clean the nose as thoroughly as possible, and for this purpose careful preparation should be carried out for three or four days.

The first case of this kind was operated on fifteen months ago, and, although the number of cases done up to date is not great, the results have been satisfactory and encourage the further use of this form of treatment.

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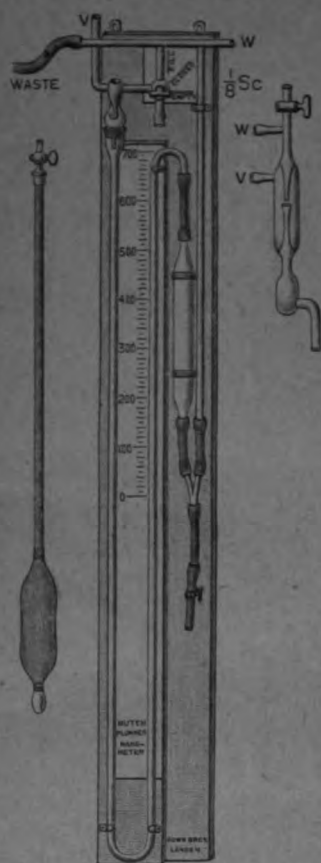
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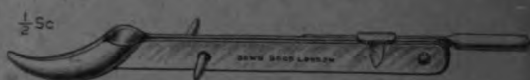
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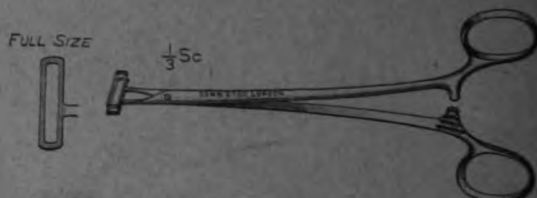
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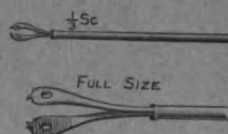
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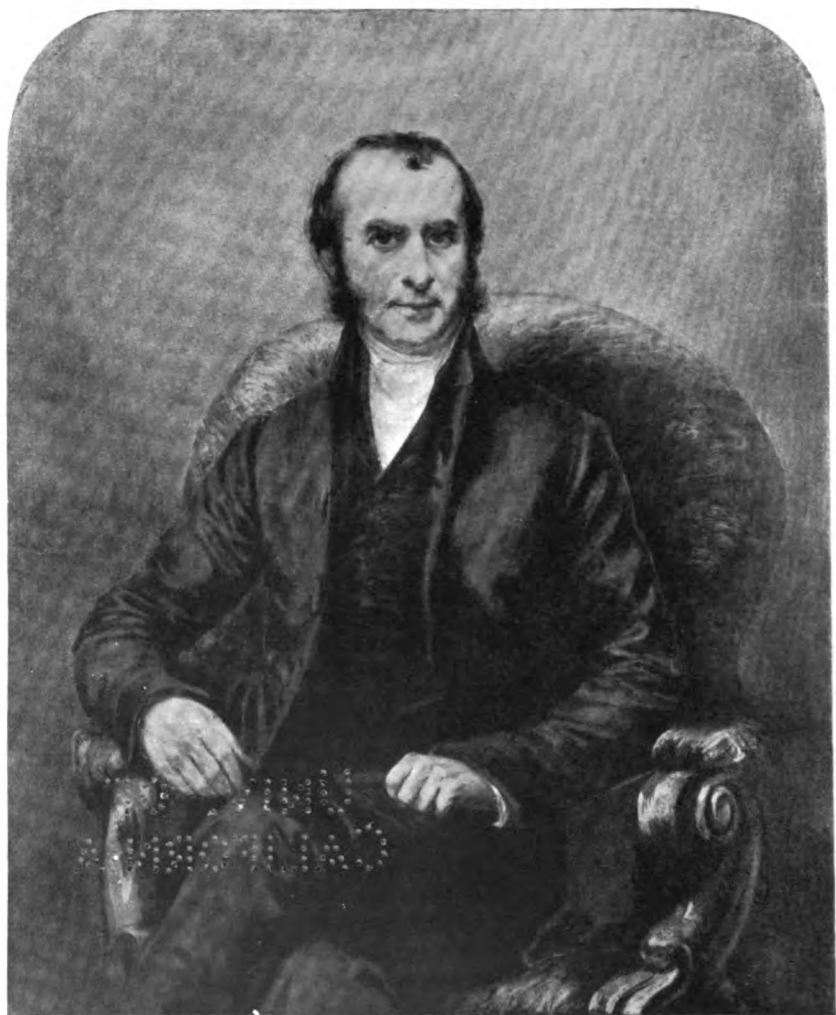
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**Thomas Hodgkin, M.D.**

Born at Pentonville, 17th August, 1795.

Died at Jaffa, 5th April, 1866.

## THOMAS HODGKIN

By SIR WILLIAM HALE-WHITE, K.B.E., M.D., Consulting Physician  
to Guy's Hospital.

THOMAS HODGKIN was born at Pentonville, on August 17, 1798. He was the third of four sons, the two elder dying in infancy. His father, John Hodgkin, a grammarian, was born at Shipton-on-Stour in 1766. He was a Quaker and came to London, living first at Pentonville and then at Tottenham, where he became a fashionable tutor. His pupils were chiefly ladies belonging to the families of wealthy citizens who lived in the neighbourhood of London. These he instructed in the classics and mathematics, but especially in the art of handwriting, in which he greatly excelled. He has left a remarkable record of his skill in his *Calligraphia Græca*. It is dedicated to his friend Dr. Thomas Young, who furnished the gnomic sentences which Hodgkin wrote in beautiful Greek characters. He died at Tottenham in August 1845. The fourth son, John, born at Pentonville in 1800, was, in his day, a well-known lawyer and a famous teacher of law, his pupils were very numerous; when forty-three years old he gave up the legal profession on account of ill-health, and devoted himself to philanthropic work. He died at Bournemouth, July 5, 1875.

It is stated in the *Dictionary of National Biography*, in obituary notices, and by Wilks, that Thomas Hodgkin was born at Tottenham, but at the foot of the portrait of him in the collection of portraits owned by the Royal Society of Medicine and here reproduced, it is said that he was born at Pentonville. This must be correct, for John, two years the junior of Thomas, was born at Pentonville, and the family lived at Tottenham after Pentonville. Further, to make sure, I wrote to Sir Rickman Godlee, whose father was Thomas Hodgkin's first cousin, and he tells me that Pentonville is the right birthplace. His mother, who married his father in 1793, was, before marriage, Miss Elizabeth Rickman, daughter of Richard Peters Rickman of Lewes.

Thomas was educated at home and became fluent in Latin, Greek, French, Italian and German. He entered at Guy's and also travelled abroad to learn medicine. He graduated M.D. at Edinburgh in 1823, and was commended for the latinity of his thesis, *De absorbendi functione*; he obtained the licentiate-

ship of the Royal College of Physicians in 1825. Fortunately, in the year 1822, he attended the clinical instruction given at the Necker Hospital by the great Laennec. Hodgkin's natural bent towards morbid anatomy was fanned by the teaching of the immortal author of *De l'Auscultation Médiate*, who also taught him the use of the stethoscope. The effect of this is seen in a paper he read before the Physical Society on the stethoscope directly after his return from Paris. There can be little doubt but that the introduction of this instrument at Guy's was largely due to Hodgkin, fresh from Paris, filled with the new knowledge he had gained from Laennec. But his travels did not end at Paris, as we know that he also visited Germany and Rome, where he lodged with Dr. Viale, surgeon to the Inquisition, a curious landlord for such a thorough-going Quaker as Hodgkin.

Happily for Guy's, in 1797 Benjamin Harrison, junior, at the age of twenty-six, became Treasurer of the Hospital. He at once began to improve it in many ways and later on turned his attention to the Medical School; his opportunity came in 1825, when the schools of Guy's and St. Thomas's, which had been previously joined, separated. Harrison at once determined to make the independent school of Guy's as good as any. He saw that morbid anatomy must be properly taught, that post-mortem examinations must, as far as possible, be made regularly on all who died in the hospital, and that a museum must be founded; he even purchased specimens out of his own pocket, and in the year 1825 appointed Hodgkin, then only twenty-seven, Curator of the Museum and Lecturer on Morbid Anatomy, which posts he held with great distinction until 1887, when Dr. Cholmeley died. This created a vacancy for the office of Assistant Physician. There were two candidates, Thomas Hodgkin and Benjamin Guy Babington. Both had their supporters; the students and some others signed a memorial in favour of Hodgkin. Both died within three days of one another, in 1866, so that their obituary notices are on the same page of the *Lancet* (April 21, 1866). Reading these shows how difficult the choice was. Finally Mr. Harrison selected Babington. It is impossible to say, at this lapse of time, what decided him. It has been suggested that he chose Babington because he disliked Hodgkin's politics; this is unlikely, for when Addison was appointed, much influence, including a recommendation from William IV, was brought to bear in favour of another candidate, but Harrison appointed Addison. In the preface to the second volume of his *Morbid Anatomy* Hodgkin alludes to his ill-health; possibly this

weighed. Anyhow we may rest assured that Harrison did what he conceived to be best for the hospital and school; the *Lancet* rightly described the success of the school as the apple of the Treasurer's eye.

Having thus failed, Hodgkin left Guy's; he had been Curator and Lecturer on Morbid Anatomy for twelve years; it is pleasant to notice that he still, after he went, retained close friendships with his late colleagues. He refers to T. W. King, who followed him as lecturer and curator, as "my much-valued friend and able successor," and, in 1840, he dedicated Volume II of his *Morbid Anatomy* to his friends Thomas Bell, surgeon dentist to Guy's, and John Morgan, surgeon to Guy's. All the work for which Hodgkin has become famous was finished, for, although the second volume of the *Morbid Anatomy* appeared three years later, the material for it was accumulated earlier than 1837. Before this year he had become well known in the scientific world; he speaks of his friends Sharpey and Joseph Jackson Lister, the discoverer of the principle of the microscope, with whom he did histological work, especially on the red blood cells. Through his father he knew Thomas Young; he also had several acquaintances among foreign members of our profession, and from the title-page of the second volume of the *Morbid Anatomy* we learn that he belonged to scientific societies in Rome, Siena, Paris, Marseilles, Brussels, Ghent, Heidelberg, Philadelphia, Massachusetts, Catania, Palermo and the Sandwich Islands. In 1836 he was offered the Fellowship of the Royal College of Physicians of London, but, like his friends Sir James Clark and Dr. Arnott, he declined it from conscientious motives.

He gave much attention to medical reforms, and especially to medical education; he was one of the earliest members of the Senate of the University of London. In 1842 he was appointed Lecturer on the Theory and Practice of Medicine to St. Thomas's Hospital School and Curator of the Museum. His introductory lecture was published as a separate pamphlet, and some of the subsequent lectures appear in the *Medical Gazette*, vol. 31, 1842-43. They are very diffuse, and it is difficult to imagine that they fixed the attention of the audience. He held this appointment but a short time, which seems to show that Harrison was right in not selecting him for the vacancy at Guy's.

He was Consulting Physician to the Dispensary for Diseases of the Skin, and in 1844 published an open letter to the Lord Mayor in favour of establishing this Institution in Bridge Street, Blackfriars.

Neither his appointment at Guy's nor that at St. Thomas's, forbade private practice; we come across patients whom he attended. Early in his career he lived in New Broad Street; in 1833 he was at 50 Finsbury Square; in 1840 at Lower Brook Street; in 1850 at Bedford Square. But he, like several other distinguished physicians, was not successful in private practice; his good-nature made him careless about money; some refused to consult him because he would not take any fee. The tale is told that he sat up all night with a very wealthy man, who was ill and recovered. The patient was so grateful that he handed Hodgkin a blank cheque, telling him to fill it in for any amount he liked. Hodgkin entered ten pounds. The patient asked him why he put such a moderate amount. Hodgkin replied that he thought the drawer of the cheque looked as though he could not afford more. The result is said to have been that the patient was so angry that he never again asked Hodgkin for his services. In 1857 three hundred guineas was subscribed as a testimonial to Hodgkin; he would not accept it and gave the money to the Medical Benevolent College.

He was never robust, and after he left St. Thomas's he gradually gave up practice and his medical interests. Still he had many others, even a velocipede. Sir Rickman Godlee tells me he used to ride one of these machines (without pedals) from Lewes to Brighton. His natural bent of mind, his upbringing and the fact that he was a Quaker—he always dressed in the Quaker garb—turned him more and more to philanthropy. He married, in 1850, a widow, Mrs. Sarah Frances Scaife, and their house in Bedford Square was the scene of much simple hospitality to philanthropists, ethnologists and geographers. Hodgkin was at one time Vice-President of both the Ethnological and Geographical Societies, and he was also in 1838 one of the founders of the Aborigines Protection Society. His publications show his activity in all sorts of philanthropic objects; indeed his later life was devoted entirely to these. He often travelled in the East with Sir Moses Montefiore to aid Jews and relieve their miseries. While doing this he contracted dysentery, of which he died at Jaffa on April 5, 1866. Sir Moses placed over his grave an obelisk of Syenitic granite. On it is inscribed, "Here rests the body of Thomas Hodgkin, M.D., of Bedford Square, London, a man distinguished alike for scientific attainments, medical skill, and self-sacrificing philanthropy. He died at Jaffa, the 5th April, 1866, in the 68th year of his age, in the faith and hope of the Gospel.

"*Humani nihil a se alienum putabat.*



"The epitaph is inscribed by his deeply sorrowing widow and brother to record their irreparable loss."

On the obverse is the following :

"This tomb is erected by Sir Moses Montefiore, Bart., in commemoration of a friendship of more than forty years, and of many journeys taken together in Europe, Asia and Africa."

#### SCIENTIFIC WORK

The *Lancet* said of him when he died : "Few men were more beloved than Dr. Hodgkin; his truly Christian charity, his unostentatious piety, his utter self-negation won and kept the love and esteem of all who knew him."

With regard to scientific and medical achievements, the first thing to say is that, as will be shown immediately, he owes his celebrity to the chivalrous honesty of Wilks. As a disease has been called after him, he is often named with Bright and Addison, but a perusal of his work shows that he is not on the same high plane as they. Only two or three of his papers are worth remembering now, that on the Lymphatic Glands and that on Retroversion of the Aortic Valves, and perhaps that on Blood Cells that he wrote with the help of Joseph Jackson Lister. In the first he certainly did show that he had discovered a new disease, but much of the paper is quite irrelevant. Only four genuine examples are described; some that he considered to be instances of it certainly were not, and he never followed the matter up by recording a larger collection of cases, as would have been quite easy. In the second he admits that he did not originally observe retroversion of the valves, but his description of the symptoms and state of the heart is new and correct, although incomplete; the whole paper is diffuse and has to be read carefully to be sure of the author's meaning. In the work on *Morbid Anatomy* we see the same diffuseness that spoils so much of Hodgkin's writing. He showed great industry in making an extensive pathological Museum and its catalogue; the labour must have been great, but the specimens are not nearly so well described as nowadays, and the case histories are meagre.

Hodgkin had a highly scientific mind; always welcoming any new discovery, he immediately appreciated the stethoscope, although his elders derided it. He learnt to use the microscope and worked at it with Joseph Jackson Lister. He called particular attention to the discovery by Babbington that it was possible to look down the throat by means of a reflecting mirror in the mouth; he refers to this instrument as a

“laryngoscope.” He perceived and helped to make known the new teaching of Addison on the nature of pneumonia. He was not frightened by Currie’s book on the treatment of fever by cold baths, but quickly recognised its value and urged it. Readers of his *Morbid Anatomy* will, as Wilks says, be struck with the fact that the doctrine of evolution, then appearing through the mist, did not alarm him.

It must always be put to his credit that he not only created a museum, but did as much as any Englishman to show the importance of *Morbid Anatomy*, and he had as wide a knowledge of this subject as anyone living at his time. He was determined to make his department one of the best in the world, for we find him saying in a lecture, “I shall conclude by assuring you that it will be my constant aim—whether I may be fortunate enough to reach the mark or not—to co-operate with those who are strenuously endeavouring to render the school of Guy’s Hospital the first medical school in the kingdom.” Nothing has come down to us to show whether he was an eloquent teacher or whether he had the happy knack of inspiring enthusiasm in others to work at his subject. Perhaps it is justifiable for us at Guy’s to wish that Hodgkin had not had his mind so much occupied with other matters than medicine. We know that while Lecturer on *Morbid Anatomy* he founded the Aborigines Protection Society. A reference to his writings at the end of this memoir shows that during the same period he worked hard at other philanthropic matters, and considering his upbringing and his relations, these affairs must have claimed much of his attention. Indeed he seems to have played three parts, that of a scientific physician and morbid anatomist; that of a reformer of medical abuses and medical teaching; and that of a busy, active philanthropist. It is highly probable but that for the two last he would have attained greater eminence in the first.

#### “HODGKIN’S DISEASE”

Hodgkin’s fame chiefly rests on a paper by him entitled “On some Morbid Appearances of the Absorbent Glands and Spleen.” It was read on January 10 and 24, 1832, before the Medical and Chirurgical Society, by which name the present Royal Society of Medicine was then known. It will be found in the *Medico-Chirurgical Transactions*, vol. 17, p. 68. He was not then a member of the Society; his paper was presented by Robert Lee, M.D., F.R.S., secretary to the Society.

The author begins by saying that the morbid alterations of

structure he is about to describe are probably familiar to many practical morbid anatomists, but, as they have not been made the subject of special attention, he is induced to bring forward a few cases.

The first, a boy of nine from Lazarus Ward, showed at the autopsy many pleuritic adhesions, tubercle of both lungs, tubercular peritonitis, tubercles in the liver and spleen, and enlargement of the bronchial and abdominal lymphatic glands.

The second, a boy of ten, was under Dr. Bright in Luke Ward. During life the spleen and the glands on both sides of the neck were observed to be enlarged. These after death were described thus: "The glands in the neck had assumed the form of large, smooth ovoid masses, connected together merely by loose cellular membrane and minute vessels: when cut into they exhibited a firm cartilaginous structure of a light colour and very feeble vascularity, but with no appearance of softening or suppuration." The bronchial, mediastinal and some of the abdominal glands were in the same condition. The liver was healthy. "The spleen was enlarged to at least four times its natural size, its surface was mamillated, and its structure thickly sprinkled with tubercles, presenting the same structure as the enlarged glands already described."

The third was a severe case of syphilis in a man aged thirty from Naaman Ward. He was probably poisoned by over-active mercurial treatment. After death, evidence of pulmonary phthisis was found and some of the lymphatic glands in the body were enlarged.

The fourth was a man aged fifty, under Dr. Addison in Clinical Ward. "The most remarkable feature in his case was the great enlargement of nearly, if not quite all of the absorbent glands within reach of examination, but more especially in the axillæ and groins. Those at the side of the neck were scarcely less so. Most of these glands . . . were of about the size of pigeons' eggs . . . smooth rounded . . . moderately firm." "On post-mortem examination the glands were prodigiously enlarged, smooth, of whitish colour both outside and on section, of the consistence of the testicle, slightly translucent, uniform throughout, exhibiting no trace of partial softening or suppuration. The alteration seemed to consist in an interstitial deposit from a morbid hypertrophy of the glandular structure itself, rather than in a new or adventitious growth." All the lymphatic glands in the body were in this condition. The liver was very large. The spleen was very greatly enlarged; "an infinite number of small white nearly opaque spots were seen pervading its substance."

The fifth was a male patient of middle age. He had long been in ill health; he was emaciated, the glands in the neck were enlarged and to a less extent than those in the groin. On post-mortem examination the lungs showed that he had suffered from lobar pneumonia. There was much serous fluid in the abdomen. The liver weighed upwards of seven pounds. Its form and the smoothness of its surface were little if at all altered. The spleen was four or five times the natural size; the cellular structure, interspersed through the parenchyma, was more conspicuous than is usual, in some parts appearing in the form of specks, in which it was soft and easily broken down. The absorbent glands accompanying the aorta were greatly enlarged, some equalling the size of a pullet's egg.

Case six was that of a man aged fifty, admitted to the hospital under Dr. Bright. He had large tuberosc swellings of considerable firmness on both sides of the neck, in both axillæ and in both groins. The glands in the neck became swollen two years ago, not long after the other swellings appeared. At the autopsy it was found that the tumours were enlarged absorbent glands. Many were found similarly enlarged in the chest and abdomen. Serous fluid was present in the pleural and abdominal cavities. The liver was small; it contained two or three white tubercles. The spleen was of moderate size, free from any adventitious deposit, a fact worthy of remark, as in very many cases of glandular disease bearing resemblance to the present case, this organ has been affected, and generally tubercular. The tumours which formed the most striking feature of this case differed little in firmness, varied in size from a horse bean to a hen's egg, were round or ovoid, invested by a thin membrane, smooth externally. Their texture was uniform throughout, they were pale or slightly translucent, and showed no evidence of cysts, suppuration or softening.

This is an abbreviated account of all Hodgkin's cases. He remarks that they agree in the remarkable enlargement of the absorbent glands, and that this enlargement appeared to be primitive rather than the result of irritation propagated from some inflamed texture. The glands showed no sign of inflammation. The enlargement consisted of a pretty uniform texture, and to be the consequence of a general increase of every part of the gland rather than of a new structure. Another circumstance which arrested his attention was that in all cases except one the spleen was diseased, and in some instances thickly pervaded with bodies of various sizes, in structure resembling that of the diseased glands. He considered that

there was a close connection between the derangement of the glands and that of the spleen, which was a posterior effect.

Then there follows the description of a case communicated to him by Dr. Carswell. Whether it is a case of what we now know as Hodgkin's disease is very doubtful. The patient only lived three or four months after the enlargement of the glands was first noticed. Some had an appearance resembling a "mixture of equal parts of brain and blood." In others there was much hæmorrhage and coagulated blood.

Next Hodgkin gives a very brief account of two patients whose lymphatic glands were enlarged, but no post-mortem examination was obtained. The paper concludes with a description of some unusual morbid appearances found in the spleen, but this is a separate communication without bearing on the cases of enlarged lymphatic glands.

It is not surprising that this communication attracted very little attention. The title of it did not suggest a new discovery; not all the patients whose lymphatic glands were enlarged were examples of the same malady. Of the cases with a post-mortem examination, only four were instances of what we now know as Hodgkin's Disease (Wilks, *Guy's Hospital Reports*, Series III. vol. xi. p. 57). The case quoted from Carswell was probably an example of sarcoma, and the cases of splenic disease which occur at the end of the paper have no bearing on those which have gone before. Hodgkin could hardly have complained if his discovery of a new disease had never been recognised, and he took no further trouble in the matter.

But he was fortunate, for Bright, with his wonderful powers of observation, saw that a hitherto unknown disease had been described, for he wrote, when speaking of disease of the spleen: "There is another form of disease which appears to be of a malignant character, though it varies from the more usual forms of malignant disease, and which has been particularly pointed out by Dr. Hodgkin as connected with extensive disease of the absorbent glands. . . . The whole of these absorbent glands, or large masses of them, become large and firm, without any tendency to suppuration . . . and at the same time the spleen becomes more or less completely infiltrated throughout its whole substance, with a white matter of almost the appearance of suet." (*Guy's Hospital Reports*, Series I. vol. iii., article "Abdominal Tumours." This article was reprinted by the New Sydenham Society and published as "Clinical Memoirs on Abdominal Tumours and Intumescence," by Richard Bright, London, 1860. The above quotation is to be found on p. 152.) This reference, buried in the middle of a

very long article, did not bring Hodgkin's discovery to light of day, but again he was lucky.

Wilks in 1856 wrote a paper entitled "Cases of Lardaceous Disease and some Allied Affections" (*Guy's Hospital Reports*, Series III. vol. ii. p. 108). Hidden in this long communication, with its unarresting title, is Wilks' rediscovery of the disease which Hodgkin had been the first to describe in 1832. On p. 114 we find this group: "Class V. Cases of a peculiar Enlargement of the Lymphatic Glands, frequently associated with Disease of the Spleen." On p. 128, "The disease might with propriety have been discussed independently, but we have brought it forward here in connection with lardaceous disease, because sometimes found with the latter and undoubtedly having some close affinity with it." Readers of this paper will see that in it we have the discovery of an independent disease of the lymphatic glands, but we should not nowadays think it had any connection with lardaceous disease. Wilks speaks of its not being "yet recognised under the ordinary forms of disease," and he gives a far superior description to that originally written by Hodgkin. He says: "The enlargement of the glands is in most cases gradual . . . and, affecting only part of the glandular system, no marked symptoms ensue, but as time tends to its development in the thoracic and abdominal glands, a slow prostration ensues, terminating in death. The glands often reach enormous size, a bunch of them often being composed of separate tumours each the size of an egg. . . . They are recognised by their peculiar elastic feel . . . they constitute distinct tumours easily separable from each other. . . . When incised their appearance is altogether peculiar, being of a yellowish colour, and having a soft, translucent aspect . . . they are remarkably tough . . . the cut surface is quite uniform . . . the spleen which contains the suet-like substance. . . . The symptoms appear to be only those of anæmia, prostration and final exhaustion."

Wilks makes it quite clear that after he had written the above paper, led by reading Bright, he found Hodgkin's description; he concludes thus: "It is only to be lamented that Dr. Hodgkin did not affix a distinct name to the disease, for by so doing I should not have experienced so long an ignorance (which I believe I share with many others) of a very remarkable class of cases."

As with the discovery, so with the rediscovery of Hodgkin's Disease, it was buried in a long paper treating of other matters, but Wilks was determined to bring it out into the open, so five years later he wrote a second article in the *Guy's Hospital Reports*

(Series III. vol. xi., 1865), entitled "Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkin's Disease), with remarks." Referring to his previous paper he says: "Although my observations were at the time original, I had been forestalled by Dr. Hodgkin, who was the first, as far as I am aware, to call attention to this peculiar form of disease." Then there follows a description of fifteen cases. From 1865 onwards Hodgkin's disease has been allowed to be a distinct clinical entity. We owe its discovery to Hodgkin, we owe its rediscovery to Wilks, who, directly he found that the disease had been recognised before, drew attention to the original description and named it after the original discoverer. As far as the merit of the discovery of the malady goes, it might just as well, or even better, have been called Wilks' disease, for he gives many more cases and a more perfect description, and inasmuch as Hodgkin's original article might never have been disinterred, we are under a deep debt to Wilks.

#### RETROVERSION OF THE AORTIC VALVES

On February 21, 1827, Hodgkin read before the Hunterian Society a paper called "On Retroversion of the Valves of the Aorta." A continuation of it with the same title was read before the Society on February 18, 1829. We easily see that he disclaims any originality for his observation that the valves can be in this condition, for the paper is in the form of a letter, thus:

"9 *New Broad Street*, 6.2.27.

"My dear Friend (C. Aston Key), Thou wilt probably recollect having pointed out to me, a few months ago, a particular state of the valves of the Aorta, which, by admitting of their falling back towards the ventricle, unfits them for the performance of their function. . . . The specimen No. 1422, in the collection at Guy's Hospital, the one in which retroversion of the valves was first observed by thyself, exhibits this derangement in a well-marked manner."

The second paper begins "My dear Friend, C. A. Key." Both are published in the *London Medical Gazette*, March 7, 1829. Hodgkin describes the affection of the valves, and notes that it is often worse in the neighbourhood of the coronary arteries. He is aware that Hunter had put up in his Museum a specimen showing this condition of the valves. At first he thought that it was characteristic that no see-saw murmur was present, but as he found a case in which it was heard he modified this opinion and concluded that "in the majority of

instances there is no *bruit de scie* accompanying retroversion of the valves." This opinion has certainly not been confirmed by subsequent experiences; still it is right to state that Hodgkin finally says: "In diseases of the aortic valves, auscultation often detects a prolonged and perverted sound, such as has been compared to the stroke of a saw, the puff of a pair of bellows or the action of a rasp." He observed the pulsation of the carotids, he records that a see-saw murmur may be heard there and a thrill felt in the pulse, and he notes too the difference between the pulse of aortic and of mitral disease. "In affections of the aortic valves there is generally no irregularity or intermission of the pulse. . . . In derangement of the mitral valve, the beat of the heart cannot be better described than by the term tumultuous. It baffles all attempt to analyse its rhythm." He notices too that, whilst in some varieties of cardiac disease, venesection is beneficial, in aortic disease "depletion seems to aggravate rather than to relieve the distress of the patient." He records the hypertrophy of the heart, and especially the dilatation and hypertrophy of the left ventricle, which is associated with aortic disease. He was disposed to refer retroversion of the aortic valves to a mechanical cause, such as sudden exertion, but he was aware that such a cause would be more easily operative if the valves were previously diseased.

It is extraordinary that these papers attracted no attention when published, for they give an excellent, although incomplete, account of aortic disease five years before the publication of Corrigan's celebrated paper in the *Edinburgh Medical and Surgical Journal*, April 1882. Wilks called them to the notice of the profession ("Note on the History of Valvular Diseases of the Heart," *Guy's Hospital Reports*, Series III. vol. xvi. p. 211, and "An Account of Some Unpublished Papers of the late Dr. Hodgkin," *Ibid.* Series III. vol. xxiii. p. 65), but still no one pays attention to them. They are not mentioned in the extensive bibliography at the end of the article on "Diseases of the Aortic Area of the Heart," in the last edition of Allbutt and Rolleston's *System of Medicine*. Hodgkin laid no claim to be the first to observe the fact that the aortic valves can be retroverted, but he was the first to write a proper account, both clinical and pathological, of aortic valvular disease.

#### BOOKS ON MORBID ANATOMY

Hodgkin's only book of any size is *Lectures on the Morbid Anatomy of the Serous and Mucous Membranes*. Volume one



was published in 1836; volume two, part one, in 1840. The *Dictionary of National Biography* wrongly states that both volumes were published in 1836. The other part of the second volume was never published. Although the serous and mucous membranes are specially mentioned in the title, there are so many lectures on what the author calls appended subjects, that the book is a general treatise on Morbid Anatomy. It is an admirable work, showing the wide first-hand knowledge the author had of his subject, and we can also easily see that he had read widely. In the Preface he says: "At the time when I commenced the study of the medical profession, a strong bias in favour of the pursuits of Pathological Anatomy not only influenced my course of study in London and Edinburgh, but prepared me to receive, with peculiar interest, the instructions and demonstrations of Laennec, at the Hôpital Necker and of Rostan, at the Salpêtrière; as well as to witness the numerous inspections at the Hôpital de la Charité, which were at that time principally performed by Professor Andral, then a student, and laboriously engaged in collecting the mass of valuable facts which he has since published in his *Clinique Médicale*. These advantages, with others of less moment, subsequently enjoyed in Italy and elsewhere, may be mentioned as circumstances which led me to undertake, with peculiar interest, the office of inspector of the dead at Guy's Hospital; together with the charge of the Museum. . . . In this country, Morbid Anatomy had not been made the subject of a regular Course of Lectures, but had been taught incidentally in the Lectures on Special Anatomy, Surgery and Medicine. In 1827 I began to lecture on this subject." It is interesting to notice that he specially acknowledges the help of his excellent accomplished friend John Blackburn. This John Blackburn was an able man who died young; he founded the Clinical Reporting Society. As Hodgkin had been appointed Curator of the Museum and Lecturer on Morbid Anatomy in 1825, it apparently took him two years to prepare his lectures.

It is impossible to epitomise the 900 pages of this work; even now it is excellent reading and shows the author to have been an admirable observer. Even snakes and tortoises were examined post-mortem, and the effects of arsenic on horses was recorded. The introductory lecture has to do chiefly with the rise and progress of the study of Morbid Anatomy and might with advantage be consulted to-day. Not many lecturers give a lecture with such a striking title as "On the Colours of Animal Tissues." We see throughout the powerful influence of Laennec, who, after Morgagni, did as much as anyone to

put *Morbid Anatomy* into the high position which it ought to hold in medicine.

Hodgkin's book had not a wide circulation; many libraries to-day do not contain a copy, and it is rare to find it in a list of second-hand books. The reasons for its want of popularity are many. Four years separated the second volume from the first; the work was never completed; Matthew Baillie's *Morbid Anatomy*, that famous, well-written, concise book which had been translated into French, German and Italian, occupied the field, many editions of it appeared, some about the same time as Hodgkin's work, which had no illustrations, whilst Baillie published an atlas of pictures of morbid conditions. Hodgkin's was a diffuse, big book, which in many places wanders from the subject of *Morbid Anatomy*; few would probably have time to read it right through. Indeed he says that one reason for its publication was that it was to contain more detail than Baillie's. Thus it appealed chiefly to morbid anatomists, and although Morgagni, Laennec, Baillie and others had preached, nevertheless in 1886 the great bulk of the medical profession were ignorant of morbid anatomy, nor did they care to know anything about it. The review in the *Medical Gazette* was favourable.

The only other considerable book by Hodgkin was "*A Catalogue of the Preparations in the Anatomical Museum of Guy's Hospital*." Arranged and edited by desire of the Treasurer of the Hospital and of the teachers of the Medical and Surgical School by Thomas Hodgkin, M.D., 1829." From the introduction we learn that at that time the hospital contained 421 beds, and that the number of deaths each year was nearly 300, but from what Wilks tells us we learn that the number of autopsies was only about 100 annually. In 1802, if not at a still earlier period, apartments were appropriated to anatomical demonstration and dissection, and to the inspection of morbid bodies. N. Davie, a very zealous and intelligent young man, at that time filled the office of Demonstrator. After his early death his preparations were purchased by the Treasurer and presented to the hospital. These, together with several specimens met with in the hospital, and preserved by the care of Richard Stocker, formed a small collection used to illustrate lectures. In 1806, when Benjamin Travers was Demonstrator, new regulations were brought in by the Treasurer, who directed that morbid specimens found in bodies examined at the hospital should be added to the Collection. Nevertheless the additions to it were few. In 1824 T. A. S. Dodd was appointed to take charge of the specimens and to assist at post-mortem examin-

ations. As we have already seen, shortly after this there was a great development of the Medical School, and the Museum participated, so that when Hodgkin published his Catalogue four years later, the Museum contained 3000 specimens. Sir Astley Cooper gave many; the collection, formed by John Fox and Thomas Bell, to illustrate the structure and diseases of the teeth, was as good as any in the country. Joseph Towne was appointed to fashion the models which are so famous, and C. J. Canton was employed to make coloured drawings. The arrangement of the Museum was anatomical. All was due to the enlightened policy of that great Treasurer, Benjamin Harrison, who, as Hodgkin justly says, should be regarded as its founder.

The catalogue is in tabular form; the first column gives the number of the specimen, the second a description of it, the third a reference to its history, and the fourth states by whom it was presented or from where it came. It must have been an arduous task to compile it; compared with the present catalogue the descriptions are unsatisfactory.

#### PATHOLOGICAL AND CLINICAL PAPERS

In 1829 Hodgkin read a very long paper before the Medico-Chirurgical Society, "On the Anatomical Characters of some Adventitious Structures." He classifies the various kinds of cysts that are found in the study of Morbid Anatomy, he traces their relationship to malignant disease, he describes the varieties of malignant tumours and ulcers, discusses the classification of cancerous tumours, and examines what we exactly mean when we apply the term malignant to a growth. He does not announce a new discovery, and nowadays the paper seems in part to be too elementary, but we must remember the ignorance of the time. Many then failed to distinguish between hydatids and other forms of cysts. In 1843 he read two papers before the same Society; one was entitled "On the Characters and Structural Peculiarities of a Group of Morbid Growths in which Cancerous Affections are included," and the other was entitled "On the Anatomical Characters of some Adventitious Structures, being an attempt to point out the Relations between the Microscopic Characters and those which are discernible by the Naked Eye." This is noteworthy as an early example of the use of the microscope in morbid anatomy. He also gave a communication on "Adventitious Structures" before the Provincial Medical Association. The first paper involved him in an unimportant correspondence in the *Medical Gazette* for 1829.

In Volume I. of the *Guy's Hospital Reports* there is an article by him, "The History of an unusually formed Placenta and Imperfect Fœtus, and of similar examples of Monstrous Productions, with an account of the Structure of the Placenta and Fœtus by Sir Astley Cooper."

He also in the same volume wrote an account of the post-mortem appearances seen in two patients described in a paper, by Bransby Cooper, on "Retention of Urine"; he appended a note to an essay, by Ashwell, on "Pregnancy complicated with Tumours," and in the same communication is a report by him of the post-mortem findings in one of the cases; in a paper, by Hilton on "A Bony Tumour of the Face," Hodgkin writes a description of the tumour, and Bright quotes his views on malignant disease in an article on "Malignant Disease of the Liver." In Volume II. of the *Reports* is a "Description of a Remarkable Specimen of Urinary Calculus: to which are added some remarks on the Structure and Form of Urinary Calculi, by Dr. Hodgkin." This is quite a short paper, in which he discusses the lamination and shape of urinary calculi.

In 1832, when the inhabitants of this country were much agitated by the appearance of cholera, Hodgkin issued a tract, "Hints relating to the Cholera in London, addressed to the Public in General, but especially to those who possess influence in their Parishes and Districts." It is dated New Broad Street, March 7, 1832. Nowadays it would be strange for a pamphlet for the "public in general" to be prefaced with Greek and Latin quotations. Hodgkin urges the clearance and cleaning of filthy slums, he thinks that cholera patients ought not to be collected together in hospitals set aside for this disease, and he implores the Board of Health to be more active. At the end of this tract is a long letter from Hodgkin to a "Member of the Board of Health" on the first appearance of cholera at Sunderland, beginning, as was usual with Quakers, "Respected Friend." In this the author comments on the awful poverty of the starved inhabitants of the slums, and advises, as a means of alleviating unemployment, what is now recommended, namely, the making of new roads.

The British Association for the Promotion of Science requested Dr. Roupell and Hodgkin to report on the effects of Acrid Poisons. This was done in 1835; apparently the Report was the work of Hodgkin, for he republished it in 1836, with his own name, without that of Roupell, on the title-page. Nearly half is taken up with a discussion of the varying appearances of the stomach and intestines in health and as the result of post-mortem changes. It appears that two other Guy's men,

Addison and John Morgan, were working at the same subject. Only eight or ten cases are described, a few were from man, others from horses or dogs to which poisons, usually arsenic, had been given. Hodgkin never performed experiments on animals himself, not because he disapproved of them, but because he disliked doing them; no doubt he would willingly have done them if anæsthetics had been discovered during his working years. There is nothing noteworthy in the Report; drawings of the stomach were made by Canton and wax models by Towne, for the Guy's Museum. The author mentions that he was helped by Joseph Jackson Lister. When, in 1836, the Association met at Bristol, he presented an account of experiments which had been done at Guy's to find whether, by injections of mercury, it could be established that there was communication between veins and lymphatics. The results obtained were inconclusive.

In 1848 Hodgkin read before the Medico-Chirurgical Society a paper entitled "Cases illustrative of some Consequences of Local Injury." Eight are described: in some, local inflammation followed the injury; in others, malignant disease; probably some of those which the author put in the second group ought to go into the first. All were fatal, and it is suggested that the cause of death must have been the absorption of some poison formed at the local seat of trouble.

Before the same Society in 1854 a paper was read on a "Case of Distortion of the Spine, with Observations on Rotation of the Vertebrae as a Complication of Latent Curvature," by Thomas Hodgkin and William Adams. Why the first name appears is a mystery, for it is clear that the article was written entirely by Adams.

We have seen that he attended the Guy's Physical Society, where early as 1822 he read a paper on "The Application of the Stethoscope." Laennec had stated that the falling in of the chest after recovery from empyæma was due to the removal of the fluid, but Hodgkin maintained that "the contraction of organised products of inflammation" was also operative. Later on in his writing he was constantly urging the use of the stethoscope. He gave the opening address at the first meeting of the session 1827-28, and spoke boldly on "Medical Education." He said: "If, from the circumstance of my bringing forward this question, it be inferred that I consider our present system of Medical Education liable to objection, I must admit this to be the case, and confess that I regard it, more especially with regard to the general practitioner, as objectionable in nearly all its stages." He advocated a great reduction of the

period of pupilage with an apothecary, a liberal preliminary education, clinical bedside instruction in the medical wards by physicians to clerks appointed to them, and the study of morbid anatomy. Happily all these reforms have come to pass.

In 1829 in a paper on "Fatty Liver," also read before the Physical Society, he again urges the importance of the study of morbid anatomy.

His interest in medical education continued, for when he was President of the Harveian Society in 1847 he took for the subject of his presidential address, "Medical Reform," and this address was reprinted as a separate pamphlet. In the *Pharmaceutical Journal*, vol. iv. No. 1, is a long letter from him to Sir James Clark with the same title. He published "Some Observations on the Examination and Classification of Candidates," submitted to the Committee of the Faculty of Medicine of the University of London, and he was a member of the Committee appointed by the University to consider the draft of the Medical Registration Bill in 1848. On May 14, 1845, he presented to the Council of the British Association an able report, recommending the suppression of the section of Medical Science at future meetings of the Association. The reasons he urged were that this section was poorly attended and that the interests of medicine were fully provided for by the many Medical Societies in the kingdom.

Hodgkin applied his mind to other subjects than morbid anatomy and medical reform. He wrote an essay, on the occasion of Oxford making an attempt on the life of the Queen in 1840, in which he maintained that there was "a form of insanity under which individuals are led to the commission of acts of great atrocity without any of the ordinary inducements which influence the acts of human beings, and from which they receive no restraint from the considerations which tend to deter those who, however depraved, are not insane." He goes on to say that in such cases proofs of insanity drawn from the individual's acts, independently of the crime committed, may be entirely wanting.

He was a member and later Vice-President of the Ethnological Society, and read on February 28, 1849, an excellent biographical sketch of the Bristol doctor, James Cowles Prichard, President of the Ethnological Society. This remarkable man, who managed to combine the practice of medicine with great learning and profound research in ethnology, was born a Quaker, and this no doubt was, in part, the reason of the affection in which he was held by Hodgkin, who himself read a paper before the Society entitled "The Progress of Ethnology."

Together with Dr. Fisher he, in 1832, translated from the French "On the Influence of Physical Agents on Life," by Dr. Edwards. Judging from the preface, most of the translation was done by Hodgkin. The book treats of the physiology of respiration and animal heat in man and the lower animals. To the appendix Hodgkin made some additions, and he reprinted there his thesis on "Absorption," together with a long continuation of it in English, and what he calls a juvenile essay "On the Uses of the Spleen," which he had published in 1822 in the *Edinburgh Medical and Surgical Journal*. There is nothing in this which now calls for comment. He also gives us an article by Joseph Jackson Lister and himself, "On the Microscopic Characters of some of the Animal Fluids and Tissues." In this is a long account of previous views on the structure of the blood; the authors then give their own description of the red cells, which is the best written at that date. Slight references are made to the microscopic appearances of chyle, milk, pus, nerves, serous membranes, mucous membranes, cellular membranes, brain and muscle; the authors noticed the presence of striation in voluntary and cardiac muscle, and that it was absent in involuntary muscle.

He published "Lectures on the Means of Promoting and Preserving Health." A review of this in the *Medical Gazette*, 1835, vol. xv. p. 839, says: "A great deal of useful popular information connected with medical subjects is contained in this small volume. The dietetic precepts are very good and sometimes curious. Some political hints interspersed in the notes to the third lecture we could wish had been omitted; they are ill timed and on the whole we think ill judged. The lectures were delivered at a Mechanics' Institute five years ago, but of course have been revised so as to be properly adapted for present purposes." The book soon went out of print; a second edition appeared in 1841. It deserves much more praise than the reviewer gave, for it is an admirable exposition of the harm which flows from filth, overcrowding, bad sanitation, horrible houses, drunkenness—the author was not a teetotaller, and even then saw signs that sobriety was increasing—bad food, want of vaccination, lack of fresh air and exercise. He denounces chimney-sweeping by children, and his picture of the lives of seamstresses reminds us of the "Song of the Shirt." His political allusions were not a whit too strong. We must bear in mind that although the House of Commons had passed a Bill forbidding the employment of children for chimney-sweeping, the House of Lords had thrown it out with gibes and laughter. Hodgkin's book must have done much good and

should be read by those interested in the progress of Public Health.

His Quaker leanings are shown in various publications, *e.g.* a letter on negro emancipation and American colonisation, an inquiry into the merits of the American Colonisation Society, on the British African Colonisation Society, and a pamphlet on the mode of selecting and remunerating medical men for professional attendance on the poor. In this essay (1836) he tells us that many parish medical officers took much trouble to obtain the post, because doing so kept a rival out of the neighbourhood, but that the work was often either scandalously neglected or an incompetent assistant was put in to do it. The remedy suggested is that these posts should be awarded as the result of competitive examination. He also wrote a Biography of William Stroud, M.D., to whom he dedicated the first volume of the *Morbid Anatomy*, "in token of sincere regard, the result of long and proved friendship; and as a mark of unfeigned respect for his acquirements, as a learned, experienced, and able physician, as well as for his exemplary virtues as a man and a Christian."

The only writings of Hodgkin, other than those mentioned in this article, that I have been able to discover are accounts of specimens shown at Societies and several descriptions of autopsies on patients whose cases have been recorded by other authors. The longest of these is an account of the post-mortem examination of a woman on whom Dr. Blundell had performed the operation of extirpation of the uterus for carcinoma at Guy's Hospital on February 19, 1828. She lived a year afterwards and improved so much in health that she called the day of operation her "second birthday." Hodgkin found that she died from constipation produced mechanically from constriction and altered position of the bowel. Blundell speaks of "Dr. Hodgkin's talents and great accuracy in morbid dissection." Truly a remarkable case for days when neither anæsthetics nor aseptic surgery had been discovered. (*Medical Gazette*, May 23, 1829, p. 797.)



# DIET AND HYGIENE IN RICKETS IN CHILDREN OF ENGLISH CITIES\*

By J. V. C. BRAITHWAITE, M.D., Assistant Physician, Leicester Royal Infirmary; late Clinical Assistant in the Children's Department, Guy's Hospital.

THE ætiology of rickets is at present the source of such sharp controversy, and experimental evidence is so contradictory, that the clinician often finds it difficult to give rational advice on the treatment of a rickety child. Out of the many conflicting opinions, however, there have arisen in the last few years two principal schools of thought, one of which believes rickets to be a disease caused by bad hygienic surroundings, particularly lack of fresh air, sunlight, and exercise; while the other holds that the condition is primarily due to a faulty dietary in which a specific vitamin is lacking. But while a vast amount of research has been done on the ætiology of the condition, the question of the relative value of these two factors in the cure of the disease has, until recently, received but little attention. There is still a very general tendency to restrict treatment to administering cod-liver oil, while the therapeutic effects of sunlight, fresh air, and exercise are neglected. Many surgeons are still in the habit of putting rickety children into splints to prevent any movement of the affected limbs—a proceeding which is a psychological if not a physical tragedy to the developing child. The primary object of the present work, which was started in October 1921, was to determine which was the more potent remedy when acting alone.

The conclusions arrived at led the author to make a small inquiry into the ætiology of the condition. This accounts for the somewhat unusual order in which this work is arranged—therapeutics being placed before ætiology.

## HISTORICAL

Although this question of ætiology has attracted a great deal of attention during the past ten years, the disease is no new one. Glisson first accurately described it in 1650, but it

\* Thesis approved for the degree of Doctor of Medicine in the University of London. (A Grant was made for part of this work by the Medical Research Council.)

was already well known in Devon and Somerset, whence he derived his material; indeed the word "rickets" was in use there before he introduced the term "rhachitis" to denote his view of the ætiology (inflammation of the spine—*ῥάχις*). Rickets is probably a corruption of the Dorset verb "to rucket," \* which means "to breathe laboriously"; evidently the west countrymen had observed the accompaniments of respiratory and nasal catarrhs or possibly laryngismus. According to Senator, some statues of the classical age show the characteristic deformities of the disease. Until the middle of the last century, however, the question of ætiology did not excite much attention, and certainly no experimental work in this direction was recorded. Then Guérin, noting the frequency of rickets among weaned infants, claimed to have produced the disease in puppies by sudden weaning and feeding on meat. He regarded it as primarily a disease of faulty alimentation. Trousseau, while admitting faulty feeding to be a factor of great importance, regarded hygienic environment and climate as having an undoubted influence on the development of the disease. It is, he observed, "much more common in damp, cold countries than elsewhere. . . . This remark is equally applicable to man and to the lower animals. Veterinary practitioners and breeders of stock will tell you that certain animals, if shut up in damp places, become rhachitic, even when they have good alimentation." Cheadle considered the condition to be due to a lack of fat and protein in the food. The treatment of the disease among the peasant class has been from time immemorial the administration of cod-liver oil or other fish oil, but apparently it was not in use among medical practitioners until the beginning of the nineteenth century. Then two German physicians, Schenck and Ferr, published cases showing its favourable influence. In 1827 Bretonneau treated a Dutch family, on the recommendation of their father, with cod-liver oil. He was so struck by the results that he tried it on other subjects with the same fortunate effects, and he recommended it to his illustrious pupil Trousseau, and the treatment became generally accepted. Trousseau, indeed, found that butter, "fowl-fat," or "melted fat of ham" was equally efficacious. Towards the end of the last century Bland-Sutton<sup>1</sup> observed that young monkeys, if deprived of their mother's milk and fed with vegetable foods, became rickety, and he prevented the onset of the disease in lion cubs at the Zoo, among which it was very prevalent, by feeding them on milk, pounded bones, and cod-liver oil.

\* Other suggested derivations are the French word "riquet," a deformed person, and "wrakken," O.E., to twist.

## BRIEF SUMMARY OF RECENT INVESTIGATIONS

What may be called the modern history of the question began in 1908, when Leonard Findlay,<sup>2</sup> wishing to produce experimental rickets in dogs, and accepting the traditional view that the disease was caused by insufficient fat, fed them on such diets as bread and water, oatmeal and water, and rice and water. To his surprise the animals wasted and died, but no rickets was produced. Nevertheless, the control animals, fed on a normal diet, developed the disease. But when these rickety puppies were allowed free exercise, their symptoms abated and only reappeared on further confinement. The diet consisted of milk and oatmeal porridge throughout. This work has recently been confirmed by Paton, Findlay, and Watson.<sup>27</sup>

In 1912 Hopkins<sup>3</sup> published his famous paper on accessory factors in the diet. He fed young rats on a diet containing protein, fat, carbohydrate, and salts in a perfectly pure condition, and the animals wasted and died. The calorific value of this diet was satisfactory. Other rats, fed on the same diet, but with the materials in a crude condition, not only remained alive but even grew slightly. Another series of animals were fed on a diet identical with that of the first group which died, but had in addition minute amounts of fresh milk. These last animals not only remained alive but thrived and developed normally. These results, he suggested, were due to certain specific and essential accessory substances present in raw milk. He also suggested that rickets, among other diseases, might be due to a lack of these factors in the diet. Funk suggested the name "vitamins" for them. Osborne and Mendell and McCollum and Davies then demonstrated that they must be of at least two varieties—Fat Soluble "A," the growth factor, absence of which from the diet caused not only cessation of growth in rats, but also the condition known as Xerosis conjunctivæ, and Water Soluble "B," without which the animals became affected with an intense degeneration of the nerves. Holst demonstrated the existence of a third vitamin, the anti-scorbutic factor.

The influence of these discoveries on the current views of the ætiology of rickets was not long in showing itself. As has been stated above, the idea that rickets was a deficiency disease was suggested by Hopkins himself, and it was supported by a monograph by Funk (*Die Vitamine*) in 1914. In 1918 Mellanby<sup>4</sup> published the results of dietetic experiments on puppies. He found that animals whose diet contained ample

calories for growth, and in which the anti-neuritic and anti-scorbutic vitamins were present, but in which the only fat was linseed oil, all developed a disease comparable in every way with human rickets—that is to say, they developed bending of the bones, ligamental laxity, swelling of the epiphyses, lethargy, and muscular atonia. X-ray appearances and chemical analysis of the bones showed a deficiency in calcification. The addition of certain fats to the diet, particularly butter and cod-liver oil, prevented the onset of the disease in other puppies. From these results Mellanby concluded that rickets was primarily due to a lack of an accessory substance in the diet, this substance being present in meat extractives and fats, but not in linseed oil. In 1919<sup>9</sup> he brought forward further evidence in support of this contention, and put forward the hypothesis that rickets was due to the deficiency of an anti-rhachitic factor, which was identical with or had the same distribution as the growth factor, Fat Soluble “A.” Later<sup>10</sup> he found that this factor was not entirely absent from vegetable oils, although linseed oil contained very little, and cocoanut oil was powerless to prevent the onset of the disease. Excess of carbohydrate and absence of meat from the diet greatly intensified the malady. Unlike Findlay, he was unable to produce rickets in dogs by confinement *per se*.

Mellanby's careful and scientific work leaves no doubt in the mind of a fair critic that rickets in dogs can be produced at will by feeding on diets deficient in certain fats. But it does not follow that the disease in children is necessarily due to a vitamin deficiency. It is well known in any out-patient department that rickets frequently occurs in children whose diet cannot be criticised, who have been breast-fed in infancy (the mother's diet being normal), and who after weaning have had ample supplies of fresh milk, butter, and dripping. Very few children are brought up on a diet exhibiting such a grave deficiency of Fat Soluble “A” as Mellanby found necessary to produce the affection in dogs; yet rickets is one of the commonest diseases of infancy. Moreover, the children of the working classes in London almost invariably are fed on a diet which contains an excess of carbohydrate and deficiency of fat and meat, and yet the majority show no signs of rickets. Clearly there must be other factors at work.

While Mellanby was pursuing his investigations, Leonard Findlay, Noel Paton, and Margaret Ferguson<sup>6</sup> had been carrying out an elaborate and careful investigation into the social and economic factors in the causation of the disease. The work was carried out chiefly among rhachitic children in Glasgow, and was

of a statistical nature. The diets of these children showed no grave deficiency in fresh animal fats. But their hygienic surroundings were almost invariably bad. These authors particularly blamed insufficient air and inadequate exercise as being potent causes of the disease. Their views received support in America from Hess and Unger,<sup>8</sup> who were unable to produce the condition in children by feeding them on a diet of skimmed milk previously heated *in vacuo* and dried, sugar and cotton-seed oil, whereas they observed its onset in children having abundance of milk with added cream. Mellanby, it is true, found that cotton-seed oil had a mildly protective action in his dogs, but even allowing that this was sufficient to explain the non-appearance of the disease in the first group of children, it is difficult to account for its appearance in the second on any vitamin hypothesis. Huldschinsky<sup>6</sup> and Hess and Unger<sup>7</sup> also found that when the disease was present it was cured by ultra-violet rays or by direct sunlight.

Hess, McCann, and Pappenheimer<sup>11</sup> in 1921 found that lack of Fat Soluble "A" produced Xerosis conjunctivæ and dwarfing in young rats, but no rickets. In the early work on accessory substances, it will be remembered that rats were used, and although a cessation of growth, Xerosis conjunctivæ, and paralysis were produced by feeding experiments, the early workers made no reference to the lesions of rickets being present. But V. Korenchevsky<sup>14, 15</sup> produced rachitic changes in rats by feeding experiments. He found that a diet deficient in Fat Soluble "A" and calcium was more effective in causing the disease than one in which the vitamin alone was lacking. He also found that a deficiency of this factor in the diet of the parents at the time of conception or of the mother during lactation was an important secondary factor.

McCollum and his co-workers<sup>16</sup> produced rachitic changes in rats by feeding them on diets deficient in but not entirely free from Fat Soluble "A." Four of these were put on to cod-liver oil and three of them showed increased laying down of calcium in the rachitic bones. The other rat showed no response to cod-liver oil. The same workers<sup>17</sup> showed that if sufficient phosphates were present in the diet, Xerophthalmia but no rickets was produced. They suggested that Fat Soluble "A" and the anti-rachitic factor were not identical. Later<sup>10</sup> they found that rats in which the disease had been produced by dietetic measures were cured by simple starvation, a fact which Jundell<sup>18</sup> had already noticed. But the most interesting results which these workers obtained were those showing the effect of sunlight in preventing the onset.<sup>20</sup> They took eighteen

rats and put them on to a diet previously known to have produced rickets in these animals. Twelve of them were exposed to direct sunlight for a total of 242 hours over a period of 62 days—about four hours a day. The animals were then killed, and those exposed to sunlight in no case presented any sign of rickets, although they were undersized. The six controls all showed signs of the disease.

In 1922 Harry S. Hutchinson <sup>21</sup> investigated the incidence of rickets among the Indian children of the Bombay Presidency. He found the disease to be very prevalent among high-caste Mohammedan and Hindoo children, whose infancy was spent in “purdah”; that is to say, they were deprived of sunlight, fresh air, and exercise. Their diet, which consisted largely of milk and ghee, was unusually rich in the fat soluble vitamin. The lower-caste children, whose open-air activity was not restricted, were not nearly so prone to the malady. The incidence among the high-caste children was 48 per cent., whereas in the lower-caste it was only 24.9 per cent.

Recently Miss Chick and her fellow-workers <sup>22</sup> have made some most interesting observations on the incidence of rickets among children under observation in the University Kinderklinik in Vienna. The children were fed on two diets of ample calorific value, one of which (Diet I) was deficient in Fat Soluble “A.” Diet II had cod-liver oil in addition, and had considerably more protein and less carbohydrate than Diet I, and in both fresh fruit juice was given as an anti-scorbutic. No case of rickets was recorded among forty infants during the summer. During the winter and spring, however, fourteen out of fifty-one infants developed the disease, all the positive cases being fed on Diet I. Three children on Diet I who received cod-liver oil in addition did not develop the condition. The fourteen positive cases, together with eighteen others, formed the material for further work on therapy. Six cases were treated with cod-liver oil under the same conditions as obtained while the disease was developing. They all showed healing. Seven cases were treated by exposure to the rays of a Mercury Vapour Quartz lamp. These cases also all showed rapid healing. Twelve cases were given outdoor treatment, seven being exposed to direct sunlight, two being shaded from the sun, and three being exposed to the sun and having cod-liver oil. The last group showed the most rapid improvement, but all the patients were cured.

The work of these observers suggests that in the child diet is a factor of great importance in determining the onset of the condition, and that the utilisation of certain fats causes healing of the disease. But their work cannot be said to support

unconditionally the view that rickets is due to the absence of a vitamin, inasmuch as out of twenty-five infants receiving Diet I without cod-liver oil in winter, twelve did not develop any signs of the condition. The evidence as to the part played by sunlight is most striking.

The divergences between the results of various observers can in part be accounted for by taking cognisance of the fact that they have used different species for their experiments. Thus Mellanby, working with dogs, has shown that lack of an accessory factor in the diet is the probable cause of canine rickets. The workers with rats have obtained contradictory results. S. S. Zilva and his co-workers<sup>12</sup> could not produce rickets by dietetic means in pigs, nor H. M. Mackay<sup>13</sup> in kittens. The work done on children, with the important exception of the recent Vienna research, is unanimously against a vitamin deficiency having any place in the ætiology of the disease. Clinicians are rather too apt to apply the results of animal experiments to their patients without paying sufficient attention to the possibility of different species contracting a similar disease by varying causal factors.

Several suggestions, not definitely for or against the vitamin hypothesis, have been put forward. Cameron,<sup>23</sup> in 1918, suggested that the disease was due to repeated catarrhal infections during infancy, and that the bone changes were analogous to the rigid finger-nails and circular dental caries which are found in catarrhal children. Noel Paton<sup>24</sup> has shown that an abnormal destruction of lecithin would account for the phenomena. Lecithin is the chief source of blood phosphates, and if these are deficient tri-calcium phosphate cannot be formed by the bones. Moreover, if the choline moiety of the lecithin molecule is destroyed, guanidine would be produced, and this substance produces tetany when injected into animals. This is a possible explanation of the frequency of the co-existence of spasmophilia and rickets. Dodds<sup>25</sup> found that the diastase index of the urine was raised and that there was a great increase in the fat content of the fæces in "acute" rickets. He suggests the disease is due to pancreatic deficiency. However, many of his cases were three or four years of age, when it would be most unlikely for the disease to be still active; they were hospital cases, but he does not state whether they were having cod-liver oil and malt—an almost invariable custom in many hospitals. In any case I was unable to confirm his results in three cases of active rickets, all of whom were under two years of age. Eric Pritchard<sup>23</sup> thinks that the numerous causes of acidosis in children are responsible for the development of the condition, the abnormal

acid bodies fixing the calcium in the blood. But the list of causes of acidosis that he gives is so large, comprising nearly all the ills of infancy, that if his suggestion were right one would expect every child to suffer from rickets. Again, starvation has been found to exert a healing action on rickets, but it produces acidosis.

While the ætiology of the condition is so doubtful, empirical treatment is necessarily employed. Cod-liver oil has been thus prescribed for years, and recently a few physicians have recommended exposure to sunlight, fresh air, and moderate exercise as well. But no one has recorded the effects of cod-liver oil in English city infants whose exercise was restricted, and who were kept out of the sunlight and open air, nor have the effects of these hygienic measures been noted in children whose diet was lacking in Fat Soluble "A."

#### INVESTIGATION A

Eight cases of early active rickets were admitted into the children's ward of Guy's Hospital between October 1921 and June 1922. The previous diet and the hygienic environment of the home were ascertained as accurately as possible from each mother, as well as the history of the disease, the family history, and an account of previous illnesses. Each mother was particularly questioned regarding the time of appearance of the first teeth, talking, and walking. Evidence of rickets was then sought for, particular attention being paid to a history of sweating or throwing off of bed-clothes, the presence of beading of the costo-chondral junctions, the appearance of other bony deformities, evidence of muscular atonia (prominence of the abdomen, kyphosis, etc.), and the mental condition of the child. Cranio-tabes, although present in some cases, was not considered as evidence of rickets, owing to its doubtful causation. On admission each child was weighed and the standing height was measured; and as soon after admission as possible an x-ray photograph was taken of the wrists. Four cases were then put on a diet markedly deficient in Fat Soluble "A," but were allowed to run about in the open air, and were encouraged to take exercise by means of suitable toys, etc.; and four were put on a diet containing ample Fat Soluble "A," but were kept in bed in the ward with splints on their legs for nine hours in each day. In five or six weeks the standing height was again measured and the wrists x-rayed. Each child was weighed daily and the rectal temperature was recorded every morning and night. The hæmoglobin index was also recorded at the beginning and at the end of the period, but as no marked



departure from the normal was ascertained, and as treatment did not cause any alteration, the results are not given. Progress was estimated by observing the changes in height, weight, the general behaviour of the child, and the x-ray appearances. The steadiness or irregularity of the temperature chart was also noted. Even the cases where temperature has been described below as "Irregular," if they did well, showed a marked tendency to attain monothermia. It had been repeatedly observed that one of the first signs of improvement in rickets is the transformation of a considerably irregular temperature curve into one which almost coincides with the normal line.

The diets were as follows :

#### DIET I

Separated milk . . . . .	1000 c.c.
Linseed oil (" Marylebone Cream ") . . . . .	18 grams.
Margarine (containing no animal fat) . . . . .	20 "
White bread . . . . .	100 "
Cooked potatoes . . . . .	90 "
Tapioca . . . . .	20 "
Sugar . . . . .	12 "
Orange juice	
Meat extract	

Calorific value = 1095.

This diet was drawn up with the help of Medical Research Committee's Special Report Series No. 38 (Report on the Present State of Knowledge Concerning Accessory Food Factors). According to the tables given there, the diet would contain no Fat Soluble "A." Later, it is true, Mellanby found that a certain amount of this factor was present in cocoanut oil, so that the margarine (which the makers had guaranteed contained no animal fat) may have contained a small amount. But the diet contained far less Fat Soluble Vitamin than that which any child would normally have. On the vitamin theory, this should be a rickets-producing diet.

#### DIET II

Whole milk . . . . .	600 c.c.
Cod-liver oil (Norwegian) . . . . .	18 grams.
Butter . . . . .	15 "
White bread . . . . .	100 "
Cooked potatoes . . . . .	90 "
Tapioca . . . . .	20 "
Sugar . . . . .	12 "
Orange juice	
Gravy	

Calorific value = 1098.

In a few cases, when the appetites had improved considerably and the children were not satisfied with the above diets, the amount of bread was increased, and a little boiled white fish was given two or three times a week.

The children were constantly under the supervision of the Nursing Staff, and visitors were not allowed to give them any food except oranges.

The children were all residents in Bermondsey or Southwark.

#### CASES

The following patients were put on Diet I and were allowed to run about in the open air :

*Case I.*—A. N., male, aged 1 year 4 months. Admitted 4.10.21.

*Diet before admission.* Breast-fed for nine months. At present (*i. e.* just before admission) he is having one pint of milk, a small milk pudding, gravy and potatoes, and three slices of bread-and-margarine a day. Once a week he has several spoonfuls of bacon fat, and once a week bread-and-butter.

The patient gets out on an average two or three hours a day. Runs about most of the day. For three or four months he has been sleeping in the same bed as his parents. The bedroom windows are open.

*Family history.* Only child. Parents healthy.

*Previous illnesses.* Always subject to colds. Attack of diarrhoea and vomiting one month before admission.

*Teething:* commenced at 4 months.

*Talking:* at 12 months.

*Walking:* at 13 months.

*History of present illness.* Since the diarrhoea and vomiting the mother has noticed increasing muscular weakness. He sweats at night and throws off his bed-clothes. For three nights previous to admission he has had attacks of losing his breath which last for one or two minutes. He is observed to "go red, hardly to know what to do with himself," then suddenly to draw in his breath with a loud sound, after which he appears perfectly normal.

*Physical signs.* Fat, flabby child; running nose; pale and immobile; prominent abdomen; slight kyphosis; beaded ribs; enlarged epiphyses of long bones.

*Progress.* During the first two nights after admission the patient had frequent attacks of laryngismus, but for the rest of the time he was in he did not have another attack. For a week he was miserable and immobile, but by the end of a fortnight was the liveliest child in the ward, running about well, happy and noisy. He made uninterrupted progress until his discharge, nine weeks after his admission.

Height 13.10.21. 75·0 cms. (29½ inches).  
 16.11.21. 76·5 cms. (30 inches).  
 Weight 13.10.21. 9,900 grams (20 lbs. 10 oz.).  
 20.12.21. 10,900 grams (22 lbs. 11 oz.).  
 Temperature : steady.  
 X-ray : 13.10.21. Slight mushrooming of lower epiphysis  
 and blurring of outline.  
 18.11.21. Outline of bone quite clear cut.

*Case II.*—A. B., male, aged 1 year 3 months. Admitted 13.1.22.

*Diet before admission.* Breast-fed for nine months. During nursing the mother was particularly careful about her diet, having fresh meat, milk and dripping every day, and butter occasionally. Just before admission the patient was having two slices of bread-and-butter a day, one pint of milk, gravy and potatoes, and patent barley.

The patient spends most of his time indoors. He sleeps in a separate cot, with bedroom windows open.

*Family history.* First child. Mother and father healthy.

*Previous illnesses.* None.

*Teething :* commenced at 8 months.

*Talking :* just starting.

*Walking :* just starting.

*History of present illness.* For the last three months the mother considers that he has not been doing well; frequently has diarrhoea and coughs, and had bronchitis a fortnight ago. Sweats profusely, and runs at nose. Throws off bed-clothes at night, cries when picked up.

*Physical signs.* Rickety forehead; rickety rosary; prominent abdomen; upper and lower central incisors only present; nasal catarrh.

*Course.* On admission the patient could walk about five paces. Five days after admission he was pushing a wooden horse about with confidence. Ten days after admission he could walk the whole length of the ward (25 yards) unaided. Four weeks after admission he looked well, was in excellent spirits, active, and putting on weight. He did well until the fifth week after admission, when he unfortunately contracted measles and had to be discharged.

Height : 14.1.22. 74·25 cms. (29½ inches).  
 17.2.22. 77·5 cms. (30½ inches).  
 Weight : 13.1.22. 10,400 grams (21 lbs. 7 oz.).  
 17.2.22. 11,500 grams (24 lbs. 1 oz.).  
 Temperature : steady.  
 X-ray : 13.1.22. Expanded ends of long bones, blurring  
 of outline, some "cupping" and  
 "lining" of juxta-epiphyseal regions.  
 16.2.22. Less cupping, strikingly increased ossifi-  
 cation.

*Case III.*—R. L., male, aged 1 year 9 months. Admitted 19.4.22.

*Diet before admission.* Breast-fed for one year. During lactation mother had meat once a day, and dripping twice a day. Now the patient has Nestlé's milk, gravy and potatoes, bread-and-butter, one egg, greens, bacon fat, cocoa and tea every day.

The patient only gets out for about two hours a day. He sleeps in a separate cot; the bedroom window is stated to be kept open.

*Family history.* Parents healthy. Two other children, one of whom died of pneumonia; the other is at present suffering from diphtheria.

*Previous diseases.* Pneumonia when 2 months old; measles when 9 months.

Teething started at 9 months; now has 11 teeth, which appeared irregularly.

Talking: just starting.

Walking: began at 1 year 4 months.

*History of present illness.* Has had cough for three months. Mother has noticed that he is restless and sweats at night, and throws off his bed-clothes. Occasional vomiting; at present is suffering from diarrhoea.

*Physical signs.* Flabby, pale child. Marked "rickety rosary"; square head; dumb-bell wrists; rickety curvature of tibiae; slight kyphosis.

*Course.* The diarrhoea which the patient was suffering from on admission ceased in ten days. However, he had several bouts of pyrexial catarrh, and, probably owing to this, failed to put on weight. But he became considerably more active and mentally alert during his stay in hospital.

Height: 19.4.22. 78.5 cms. (29 inches).

23.5.22. 75 cms. (29½ inches).

Weight: 19.4.22. 8,750 grams (18 lbs. 3 oz.).

23.5.22. 8,400 grams (17 lbs. 8 oz.).

Temperature: irregular.

X-ray: 20.4.22. Expansion of ends of radius and ulna. Blurring of outline. Some "lining."

23.5.22. Expansion not nearly so marked. Outline quite clear cut. Lining disappeared from large bones.

*Case IV.*—G. H., male, aged 1 year 5 months. Admitted 29.4.22.

*Diet before admission.* For the first half-year of infancy the patient was fed on the breast, supplemented by condensed milk. Just before admission he was having 1-1½ pints of fresh cow's milk a day, two or three slices of bread-and-dripping, two or three slices of bread-and-butter, and occasionally fish and egg.

*Family history.* Three other children, who all died with "wasting." One miscarriage. Parents healthy.

*Previous diseases.* Bronchitis at 4 months. "Has always got a cough and a cold."

Teething: had not been observed.

Talking: began at 18 months.

Walking: began at 11 months.

*History of present illness.* Four months ago the patient started to fall about a great deal, and the mother noticed that the wrist-bones were becoming prominent. He is restless and sweats at night, and throws off his bed-clothes.

*Physical signs.* Marked beading of ribs; Harrison's sulcus; dumb-bell wrists; curved legs; kyphosis; pot belly; flabby muscles.

*Course.* The patient became very much more active under treatment. The muscle tone improved considerably, the appetite increased, and the child showed a considerable increase in mental alertness.

Height: 29.5.22. 78 cms. (28½ inches).

28.6.22. 78.75 cms. (29 inches).

Weight: 30.5.22. 9,050 grams (18 lbs. 18 oz.).

28.6.22. 9,450 grams (19 lbs. 11 oz.).

X-ray: 29.5.22. Expansion, cupping and deformity of ends of both radius and ulna. Irregular, blurred outline.

28.6.22. Marked improvement in ossification; lessened deformity; no blurring.

The following cases were put on to Diet II and were kept in bed in the ward with splints on their legs for nine hours a day:

*Case V.*—G. C., female, aged 1 year 4 months. Admitted 6.10.21.

*Diet before admission.* Artificially fed on cow's milk in infancy. Just before admission she was having one pint of milk, two slices of bread, gravy and potatoes, a little meat and fish, and margarine.

The patient has been in the open air for three or four hours every day. She runs about the tenement in which she lives. She is said to sleep in a separate cot, and the bedroom windows are kept open.

*Family history.* One other child, well. Parents healthy.

*Previous illnesses.* None.

Teething: began at 9 months.

Talking: began at 12 months.

Walking: just starting.

*History of present disease.* The mother states that the patient was doing well until two months ago, when she became restless at night and started to talk in her sleep. She is seen to sweat and continually throws off her bed-clothes. Her nose is always running. Three weeks before admission she had two convulsions.

*Physical signs.* Immobile; beaded ribs; enlarged epiphyses of long bones; marked rickety deformity of legs; kyphosis.

*Course.* The weight remained stationary for one week after admission, but then commenced to rise steadily, and the patient became very fat. Her mentality remained slow, and no attempt at voluntary movement was made. She did not resent the application of splints.

Height : 13.10.21. 77.5 cms. ( $30\frac{1}{2}$  inches).

17.11.21. 77.5 cms. ( $30\frac{1}{2}$  inches).

Weight : 13.10.21. 9,500 grams (19 lbs. 13 oz.).

17.11.21. 11,300 grams (23 lbs. 9 oz.).

Temperature : irregular.

X-ray : 6.10.21. Expansion of bones, cupping, and deficient ossification of lower ends of radius and ulna, and of metacarpal and phalangeal bones. Blurring and irregularity of outline.

22.11.21. Some increase in ossification, but outline still blurred and irregular.

After being under these conditions for six weeks, the patient was allowed to run about in the open air. At first no attempt was made to walk, but she was trying hard in three days, and in a week was walking well. Her general condition rapidly improved. A month after her being allowed out, x-rays showed a marked increase in ossification, and a sharpening of the outline of the affected epiphysis.

*Case VI.*—R. W., male, aged 1 year 4 months. Admitted 4.12.21.

*Diet before admission.* Bottle-fed since birth with diluted cow's milk. Just before admission he was having  $1\frac{1}{2}$  pints of boiled cow's milk, one slice of bread, greens, potatoes and gravy daily.

*Family history.* Six other children, well: twin brother of patient died from wasting at three months. Parents healthy.

*Previous illnesses.* Repeated attacks of bronchitis since birth.

Teething : began 11 months.

Talking : just starting.

Does not walk yet.

*History of present illness.* When the patient was eleven months old the mother noticed that the left leg was becoming "bandy." This has gradually become more apparent and the other leg is now affected. For the same period the patient's head has sweated copiously, and he has thrown off his bed-clothes. He has suffered from a cough all the time.

*Physical signs.* Marked muscular atonia; pale; prominent abdomen; slight Harrison's sulcus; beaded ribs; some bowing of legs; kyphosis; rhonchi heard in both lungs.

*Course.* The patient kept on getting catarrhs. His spirits were good, but he remained immobile. Owing to an epidemic

of influenza the ward had to be closed five weeks after his admission.

Height : 6.12.21. 76.25 cms. (30 inches).

5.1.22. 76.25 cms. (30 inches).

Weight : 4.12.21. 8,850 grams (18 lbs. 7 oz.).

5.1.22. 8,600 grams (17 lbs. 15 oz.).

Temperature : irregular.

X-ray : 9.12.21. Irregularity and blurring of outline of both radial and ulnar epiphysis. Some cupping of lower end of ulna.

5.1.22. Condition unchanged.

*Case VII.*—J. C., male, aged 1 year 9 months. Admitted 19.1.22.

*Diet before admission.* Breast two months, followed by dried milk. Has recently been having one pint of cow's milk, gravy and potatoes, six slices of bread, and 2 oz. of butter every day, and occasionally an orange and a banana.

The child gets out for two or three hours out of the twenty-four, but only at night. He sleeps in a separate cot, with bedroom windows open.

*Family history.* Two other children, well. Parents healthy.

*Previous illnesses.* Broncho-pneumonia at 2 months. Fall with (?) slight concussion 1 month ago.

Teething : commenced at 12 months.

Talking : is just beginning.

Walking : started at 1 year 8 months.

*History of present illness.* The patient has not been doing well for three months. He sweats at night and throws off his bed-clothes. He cries on being picked up.

*Physical signs.* Kyphosis; cranial bossing; beaded ribs, with considerable eversion of lower costal margin; abdomen prominent; rhonchi audible all over chest; pronounced nasal catarrh.

*Course.* The patient sweated a great deal about the head all the time he was under observation. His appetite improved, and his subcutaneous fat increased. His mental state was very changeable; often he had fits of passionate screaming. His nasal catarrh showed no improvement.

Height : 19.1.22. 72.25 cms. ( $28\frac{1}{2}$  inches).

28.2.22. 73 cms. ( $28\frac{3}{4}$  inches).

Weight : 19.1.22. 9,200 grams (19 lbs. 3 oz.).

28.2.22. 10,550 grams (23 lbs.).

Temperature : irregular.

X-ray : 19.1.22. Blurring of outline of lower radial epiphysis; some "lining" of lower ulnar epiphysis.

28.2.22. Condition almost unchanged; there is now slight "cupping" of lower ulnar epiphysis.

*Case VIII.*—M. L., female, aged 2 years 4 months. Admitted 9.8.21.

*Diet before admission.* Breast-fed for ten months. At the time of admission she was having three slices of bread-and-butter, gravy and potatoes, one egg,  $\frac{1}{2}$  pint of milk a day.

Gets out "nearly every day."

*Family history.* Seven other children all well. Twins died—one still-born, the other living fifteen hours. Parents healthy.

*Previous diseases.* Measles at 1 year 7 months. Repeated attacks of bronchitis.

Teething: started at 8 months.

Talking: at 12 months.

Walking: at 18 months. The patient did not sit up until 9 months.

*History of present illness.* The child has not done well since measles nine months ago. The mother observed that the legs were "going bandy," and that she sweated at night.

*Physical signs.* Great muscular atonia; epiphyses of wrists enlarged; marked beading of ribs and bowing of legs; prominent forehead; prominent abdomen.

*Course.* The weight of the patient increased rapidly, but for the first ten days she was miserable and rather passionate. She then became much more cheerful and her physical and mental condition showed marked improvement.

Height: 10.8.22. 77.5 cms. ( $30\frac{1}{2}$  inches).

14.4.22. 77.5 cms. ( $30\frac{1}{2}$  inches).

Weight: 10.8.22. 9,200 grams (18 lbs. 15 oz.).

14.4.22. 11,200 grams (28 lbs. 5 oz.).

Temperature: irregular.

X-ray: 10.8.22. Marked expansion and "cupping" of lower ends of bones of forearms. "Cupping" of ends of metacarpal and phalangeal bones. Irregular and blurred outlines.

14.4.22. Great increase in ossification. No "cupping." Clear-cut outlines.

#### INVESTIGATION B

When I came to Leicester in 1922 I was struck by the prevalence of rickets in the children attending out-patients at the Royal Infirmary, although their diets, on the whole, were superior to those of the London children. In the following year, when, in addition to Infirmary out-patients, I had the privilege of doing a considerable amount of Infant Welfare work, this impression was accentuated; a large number of babies whose diets were beyond reproach (except that a great percentage were bottle-fed, owing to the prevalent custom of married



women continuing to work in factories) presented signs of the disease.

It occurred to me that it would be instructive to draw up questionnaires to be answered by the mothers of the rickety children. These questionnaires were three in number. Questionnaire 1 was answered by the mothers of children with active rickets, who were suckling their babies; Questionnaire 2 by mothers of bottle-fed rickety infants; and Questionnaire 3 by mothers of children with healed rickets. The criteria of active rickets employed were beading of the ribs and sweating. The cases invariably showed other signs of the disease, such as eversion of the ribs, enlargement of the wrists, bony curvature of the legs, delayed dentition, etc., but no case was investigated which did not show the above two signs. The history of sweating in each case dated back to cool weather. Cases were considered healed which showed rickety deformities, who had a history of sweating and immobility, but in whom the sweating had ceased and there had been a marked increase in energy. Many cases of healed rickets were seen, but only in five cases could the mothers give a definite date for the commencement of improvement. Questionnaires 1 and 2 were also answered by the mothers of normal children for the purposes of comparison.

#### QUESTIONNAIRE 1

(Answered by mothers of breast-fed children suffering from rickets, and by mothers of normal breast-fed children.)

1. What is your present diet? How much animal fat do you get, and in what form do you take it?
2. How many hours in each day is the child out of doors?
3. Does the child sleep in a separate cot?
4. Are the bedroom windows open at night?
5. How many garments does the child usually wear?  
(The mother's reply was checked by inspection.)

#### QUESTIONNAIRE 2

(Answered by mothers of bottle-fed children with rickets, and by mothers of normal bottle-fed children.)

1. What is the present diet of the child?
- 2, 3, 4, and 5. As in Questionnaire 1.

#### QUESTIONNAIRE 3

1. How old was the child when the symptoms ceased?
2. At what season of the year did you notice their cessation?

3. Did you add anything to the diet or otherwise alter the food at this time?

4. Was there any alteration in the length of time the child was out of doors then?

5. Did you make any alteration in the sleeping arrangements at the time?

6. Did you remove or add any garments?

#### RESULTS OF QUESTIONNAIRES

The actual answers given to the questions will be found in Appendix II.

From time to time the accuracy of the mothers' statements were checked by the City Health Visitors.

Most of the answers were found on these occasions to be reliable, with the exception of the answers to the question about the windows being open at night. For some reason the mothers were very loth to admit that they closed their bedroom windows at night, although it was found to be a very common practice.

#### QUESTIONNAIRES 1 AND 2

Except for the question of diet, these two groups can be considered together. Twenty-three cases comprised these groups, nine of which were breast-fed and fourteen bottle-fed. Sixteen mothers of normal babies were similarly questioned for purposes of comparison—seven breast-fed and nine bottle-fed.

##### (a) *DIET (I). Breast-fed babies*

In only one case (Case 1) was there any deficiency of animal fat in the diet of the mother. Fresh milk was taken plentifully. In eight cases the mother knew exactly how much milk she took each day, and the average of these was 1·4 pints. Every mother had meat once a day, eight had butter every day, three had dripping, six had cheese. The diets of the seven mothers of normal children were very similar to those of the mothers of rickety children. They all had milk. In five cases in which the amount of milk taken was known the average was 1·3 pints—a little less than the first group. All these mothers had butter, two had dripping, only one had cheese.

The diets of the mothers of rickety babies were slightly better than those of the mothers of normal babies.

##### (II). *Bottle-fed babies*

Among the fourteen patients, one only (Case 2) was fed on a diet deficient in fat; three (2, 3 and 4) had an excess of carbo-

hydrate in the diet. Eight patients were fed on fresh milk, partially or wholly. One infant was fed on boiled milk, and one on sterilised milk (each of these had butter in addition); three children had dried milk; six children had butter; one child had dripping and bacon fat. Of the nine normal bottle-fed infants, six had fresh milk, and three had dried milk; one case had added butter, and the same case (1) had excessive carbohydrate.

In these twenty-three cases it is obvious that diet had no effect in the production of the disease.

(b) *Hours out of doors*

The difference between rickety and non-rickety babies in this matter was striking. Of the twenty-three rickety children, thirteen had an average number of hours out of doors of less than four per diem. The average number of hours out for the whole twenty-three was 3·7. Of the sixteen normal children only one was out less than four hours a day, and the average number of hours in the open air was 6·8.

(c) *Sleeping arrangements*

Nine of the rickety infants slept with their parents, fourteen in a separate cot. Two of the normal infants slept with adults, fourteen by themselves.

(d) *Clothing*

The majority of the rhachitic children were over-clothed. Not only was the number of garments increased, but the character of the clothing was faulty—flannelette and tight stays being very popular. The average number of garments worn by rickety infants was 5·85, whereas that for the normal was 4·4.

(e) *Nocturnal ventilation*

Mothers were almost unanimous in saying that the windows were kept open at night. Most of them were not telling the truth, according to the testimony of the Health Visitors.

### QUESTIONNAIRE 3

Only five cases could be obtained in which the mother could say definitely when she noticed the disappearance of the symptoms of active rickets.

(a) *Season*. The symptoms ceased in the spring in two cases, in summer in the other three.

(b) *Change of diet*. In three cases no change was made in the diet at the time of improvement. In one case meat was added, and in one case meat and cod-liver oil.

(c) *Change in time out of doors.* In three cases the number of hours out was considerably augmented.

(d) *Change in sleeping arrangements.* In one case a separate cot was obtained just before the disappearance of the symptoms.

(e) *Change in number of garments.* In three cases the number of clothes was lessened at the time of improvement.

In one case no change of any kind was made, either in the diet or in the environment of the child. In one case there was an increase of six hours in the time that the child was out, but no change in the diet, and in one case one garment was left off while the diet remained unchanged. In the two cases where the diet was changed, sweeping changes were made in the environment of the child.

### SUMMARY

#### *Investigation A*

The cases are briefly summarised in the following tables :

TABLE I

CASES I-IV. (ON DIET DEFICIENT IN FAT SOLUBLE "A," BUT ALLOWED TO RUN IN OPEN AIR)

Case.	Time under observation.	Change in height.	Change in weight.	Temperature.	X-ray.
I.	9 weeks	+ 1.5 cms.	+ 1000 grams	Regular	Improvement
II.	5 weeks	+ 3.25 cms.	+ 1150 grams	Regular	Striking improvement
III.	5 weeks	+ 1.5 cms.	- 350 grams	Irregular	Improvement
IV.	4 weeks	+ 0.75 cm.	+ 400 grams	Irregular	Striking improvement

Although Case III did not put on weight, his growth and bony changes were satisfactory. On the whole, these cases did well. One of the most striking points was their rapid growth.

TABLE II

CASES V-VIII. (ON DIET RICH IN FAT SOLUBLE "A," BUT KEPT INACTIVE INDOORS)

Case.	Time under observation.	Change in height.	Change in weight.	Temperature.	X-ray.
V.	6 weeks	0	+ 1800 grams	Irregular	Slight improvement
VI.	5 weeks	0	- 250 grams	Irregular	No change
VII.	6 weeks	+ 0.75 cm.	+ 1350 grams	Irregular	No change
VIII.	6 weeks	0	+ 2000 grams	Irregular	Striking improvement

It should be noted that Case VIII was considerably older than the other children, that her history was longer, and that in all probability the disease was undergoing spontaneous arrest when she came under observation. Case V was subsequently allowed to run in the open, and showed rapid healing. Although the weight of these cases was usually satisfactory, they made little or no progress in growth or healing of the bones.

Of the six cases who showed improvement, four were under observation between October and the following April, thus showing that the strong sunlight of summer is not essential for amelioration of the condition.

It is fully realised that this investigation would be more complete if another four cases were observed while they were on a diet of low animal fat, and while they were deprived of exercise, fresh air, and sunlight at the same time. This, however, was not considered to be a justifiable procedure.

### *Investigation B*

The diets of the mothers of rhachitic breast-fed children did not show any marked difference from those of the mothers of normal children. The diet of bottle-fed children with rickets similarly compared very favourably with those of normal bottle-fed infants.

The hygienic management of rickety children did not compare at all favourably with that of the non-rhachitic. The number of hours out of doors each day was considerably less on an average among the rhachitic. The rickety children were also much more over-clothed than the normal.

In the five cases of healed rickets there was not one in which change in the diet alone preceded the abatement of the symptoms. In two cases hygienic changes were made without changing the diet; in two cases the diet was changed at the same time as sweeping alterations in the environment of the child, and in one case neither diet nor environment were changed before the cessation of symptoms.

### CONCLUSIONS \*

(1) That a diet rich in Fat Soluble "A" does not necessarily bring about rapid healing in human rickets, if fresh air, sunlight, and exercise are withheld.

\* Since this paper was finished Dr. Douglas Galbraith, working on somewhat similar lines, has come to similar conclusions (*Quarterly Journal of Medicine*, p. 64, July 1923).

(2) That fresh air, sunlight, and exercise cause rapid improvement in human rickets even when the diet is gravely deficient in the Fat Soluble Vitamin.

(8) That strong summer sunlight is not necessary for the cure of the condition.

(4) That diet has little influence in causing or preventing the disease in children.

(5) That unhygienic practices, particularly keeping the child indoors and over-clothing him, greatly favour the onset of rickets.

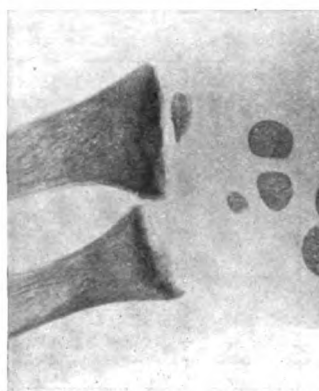
My best thanks are due to Dr. H. C. Cameron for the use of cots under his care during the first part of this work, and to Nurses Read and Cragg, Leicester City Health Visitors, for their valuable assistance in the latter parts.

# APPENDIX I

## CASE IV



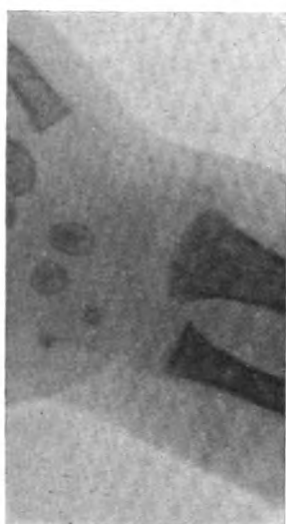
29.5.22.



28.6.22.

(After 4 weeks on diet deficient in Fat Soluble "A," but having sun-light, fresh air and exercise.)

## CASE VII

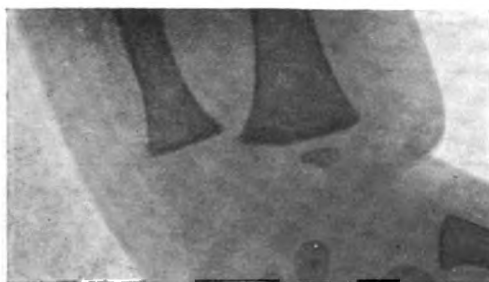


19.1.22.



28.2.22.

(After 6 weeks on diet containing ample Fat Soluble "A," but kept in bed indoors.)



Nearly normal wrist, 18 months.

**APPENDIX II**  
**RESULTS OF MOTHERS' QUESTIONNAIRES**  
**QUESTIONNAIRE I**  
**(A) Breast-fed Rickety Infants**

Case.	Age.	Diet of Mother.*	Hours out each day.	Sleeping arrangements.	Number of garments.	Windows.
1	Six months	Milk $\frac{1}{2}$ pint, margarine, dripping (alternate days), cheese, meat, bread, potatoes	2-3	With parents	4	Open
2	Seven months	Milk, butter, Virol, meat, fish, eggs, bread, potatoes	3-4	Separate cot	4	Open
3	Twelve months	Milk 1 pint, butter, dripping, meat, bread, potatoes, fruit	5	With parents	4	Open
4	Eight months	Milk $\frac{1}{2}$ pint, butter, dripping, meat, bread, potatoes, greens, fruit	3	With parents	6	Shut in cold weather
5	Eleven months	Milk 2 pints, butter, cheese, meat, bread, potatoes, fruit	$\frac{1}{2}$	Separate cot	6	Open
6	Fifteen months	Milk 2 pints, butter, cheese, meat, bread, potatoes, fruit. (Child now on mixed diet—milk 2 pints)	2-3	Separate cot	5	Open
7	Twelve months	Milk 2 pints, butter, cheese, meat, eggs, bread, potatoes	2-3	With parents	6	Open
8	Five months	Milk $1\frac{1}{2}$ pints, butter, cheese, meat, suet puddings, bread, potatoes, greens	4	Separate cot	5	Open
9	Seven months	Milk 2 pints, butter, cheese, meat, bread, potatoes, greens	$\frac{1}{2}$	Separate cot	5	Open

**(B) Breast-fed Normal Infants**

1	Six months	Milk, butter, meat, bread, potatoes, greens	6-7	Separate cot	4	Open
2	Eight months	Milk, butter, Virol, meat, bread, potatoes, greens, fruit	5	Separate cot	4	Open
3	Eighteen months	Milk $1\frac{1}{2}$ pints, butter, dripping, meat, bread, cereal food, potatoes, fruit	6	Separate cot	5	Open
4	Nine months	Milk $1\frac{1}{2}$ pints, butter, meat, eggs, fish, cocoa, bread, potatoes, greens	8	Separate cot	4	Open
5	Twelve months	Milk $1\frac{1}{2}$ pints, butter, cheese, meat, egg, fish, bread, potatoes, greens, fruit	5-6	With parents	5	Open
6	Thirteen months	Milk 1 pint, butter, meat, egg, bread, potatoes, greens, fruit	7	With parents	4	Open
7	Seven-teen months	Milk 1 pint, butter, dripping (very other day), meat, egg, bread, potatoes, greens, fruit	3	Separate cot	5	Open

\* The various ingredients were taken daily unless otherwise stated.



## QUESTIONNAIRE II

(A) *Bottle-fed Rickety Infants*

Case.	Age.	Diet.	Hours out each day.	Sleeping arrangements.	Number of garments.	Windows.
1	Ten months	Dried milk	2	Separate cot	6	Open
2	Eighteen months	Condensed milk	6	Separate cot	6	Open
3	Eighteen months	Milk 1 pint, butter, meat, bacon fat, dripping, bread (6 slices), potatoes	3	With parents	6	Open
4	Twelve months	Sterilised milk, butter, orange juice, bread	10	Separate cot	3	Open
5	Eight months	Fresh milk	7	With parents	5	Open
6	Eleven months	Fresh milk and patent barley	2	Separate cot	6	Open
7	Eight months	Fresh milk and malted food	4-5	Separate cot	7	Open
8	Six months	Dried milk	2-3	With parents	5	Open
9	Fourteen months	Fresh milk, egg, butter, gravy, bread	4	Separate cot	5	Open
10	Twenty-one months	Milk and malted food, butter, gravy, meat, potatoes, egg, bread	2-3	With parents	5	Open
11	Twelve months	Milk, butter, egg, gravy, fish, potatoes, bread (6 slices)	6	With parents	7	Open
12	Six months	Dried milk	4-5	Separate cot	6	Open
13	Eleven months	Fresh milk	3-4	Separate cot	6	Open
14	Eleven months	Boiled milk, butter, milk puddings, gravy, bread	4	Separate cot	5	Open

(B) *Bottle-fed Normal Infants*

1	Nineteen months	Fresh milk, starch food, butter, egg, gravy, potatoes, bread	7	Separate cot	4	Open
2	Eleven months	Grade A milk	8	Separate cot	4	Open
3	Six months	Fresh milk and barley water	8	Separate cot	6	Open
4	Nine months	Fresh milk	10	Separate cot	4	Open
5	Six months	Dried milk	6-7	Separate cot	5	Shut
6	Nine months	Fresh milk	6	Separate cot	4	Open
7	Eight months	Dried milk	8	Separate cot	5	Open
8	Seven months	Dried milk	6-7	Separate cot	4	Open
9	Six months	Fresh milk	7-8	Separate cot	5	Open

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## QUESTIONNAIRE III

### *Infants with healed Rickets*

Case.	Age at cessation of sweats.	Season at cessation of sweats.	Change of diet.	Change in number of hours out.	Change in sleeping arrangements.	Change in number of garments.	Change in nocturnal ventilation.
1	Twenty-four months	Spring	None	+ 6 hours	None	None	None
2	Twenty-two months	Summer	None	None	None	- 1 garment	None
3	Twenty-nine months	Spring	None	None	None	None	None
4	Twenty months	Summer	Meat added	+ 4 hours	Separate cot obtained	- 1 garment	None
5	Seventeen months	Summer	Meat, milk and cod-liver oil added	+ 2 hours	None	- 2 garments	None

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## THE TREATMENT OF AORTIC ANEURYSM BY ANTI-SYPHILITIC REMEDIES

By J. J. CONYBEARE, *M.C.*, *M.D.*, Assistant Physician and Astley-Cooper  
Student at Guy's Hospital.

ALTHOUGH an association between aortic aneurysm and syphilis had been noticed as early as the seventeenth century, it is only in the last twenty years that the real importance of syphilis as the causal factor in aneurysm has been recognised. Galen and other medical writers up to the end of the fifteenth century appear not to have been familiar with thoracic aneurysm, though those of superficial vessels were described. The first satisfactory account of intra-thoracic aneurysm we owe to Vesalius. Theophilus Bonetus<sup>1</sup> in 1700 quotes two cases recorded by Vesalius in 1557. In one of these an aortic aneurysm was found post-mortem, but the other case was diagnosed by Vesalius during life and confirmed at autopsy. The history of the case as described by Bonetus is interesting. "The patient had a fall from a spirited horse and suffered from most severe pain in the back, which failed to yield to any of the various treatments employed. At length Vesalius, who in his own time was unequalled, and indeed far superior to all, in anatomical knowledge, was summoned from Belgium. He discovered a large pulsating tumour in the region of the back and spine, which showed no evidence of inflammation, and pronounced it to be an aneurysm (*ἀνεύρυσμα*) from dilatation of the aorta." Vesalius gave a bad prognosis and the patient died of hæmoptysis shortly afterwards. Bonetus continues: "When the body was dissected the prediction of Vesalius was found to be correct. In the cavity of the aorta itself there was a very large tumour, hard and fleshy, derived from the arterial blood itself, which had protruded even through the chest wall and produced the pain and pulsation in the back." Apparently Vesalius attributed the aneurysm to the fall from a horse and does not suggest the possibility of syphilis. It is significant, however, that this description dates from the century in which syphilis began to become really common in Europe.

In 1665 the French surgeon Ambroise Paré<sup>2</sup> suggested a relationship between aortic aneurysm and syphilis. Writing

of aneurysms he says: "The aneurysms which happen in the internal parts are incurable, such as these which frequently happen to those who have often had the unction and sweat for the cure of the French disease." He then goes on to quote several cases of thoracic aneurysm, including one in a patient, who died suddenly of hæmoptysis while playing tennis. Lancisi<sup>3</sup> in 1728 laid stress on the importance of syphilis in the ætiology of the disease and even uses the term "venereal aneurysm." In 1876 F. H. Welch<sup>4</sup> noted the frequency of a history of syphilis in cases of aneurysm occurring in the British army, and found that in his series of one hundred and seventeen cases, sixty-six per cent. had previously been infected with syphilis.

Sir Samuel Wilks, writing in Hilton Fagge's<sup>5</sup> *Text Book of Medicine* in 1886, recognised that syphilis is "by no means an infrequent antecedent" in thoracic aneurysm. He lays, however, even more stress on heavy manual work and sudden strain as causal factors. In his paper on syphilitic affections of the internal organs, Wilks<sup>6</sup> quotes the case of a prostitute suffering from syphilis, in whom an abdominal aneurysm occurred, and expresses the opinion that the aneurysm was the result of the syphilitic infection.

The present-day conception of aortic aneurysm as almost invariably a manifestation of syphilis owes its origin to the general employment of the Wassermann test and to the pathological investigations on the changes in the walls of the aorta which occur in syphilis. Moreover, it is now generally admitted that not only aortic aneurysm, but also a large proportion of cases of aortic valvular disease, are dependent on syphilitic changes.

If the important factors in the production of aortic aneurysms are first of all syphilis and secondly strain, it might be expected that the war would have brought about a considerable increase in the disease. This, however, to judge by the report of the Registrar-General<sup>7</sup> for 1921, does not appear to have been the case. In Table I are given the figures showing the total deaths from aneurysm in the United Kingdom from 1906 to 1921, and also the deaths per million living persons. It will be seen that the number of deaths from the disease remained fairly constant until 1917, since which year it has shown a decline. A possible explanation of this fact lies in the increased facilities for the thorough treatment of syphilis in its primary and secondary stages, which were made possible by the introduction of the "Neo-Salvarsan" compounds and the establishment of venereal clinics. The Registrar-General's figures include deaths from

aneurysms of vessels other than the aorta, but the former are probably very few.

In spite of the recognition of the close association of aortic aneurysm and syphilis, it is remarkable that active anti-syphilitic treatment has had but little trial in the treatment of the disease. It is only in the last few years that the salvarsan group of drugs has been employed, though it is true that potassium iodide was recognised by Hilton Fagge as being of some value. Possibly the reason why salvarsan and its derivatives have been neglected is that these drugs occasionally provoke a latent syphilitic process to temporarily increased activity. This exacerbation of clinical symptoms has been long recognised and is known as the Jarisch-Herxheimer reaction; it is the basis of the provocative dose of salvarsan used in attempting to obtain a positive Wassermann reaction. Should such a reaction occur in cases with a specific infection of aorta or heart, it has been assumed that a fatal result might occur. The risk, however, is one which can be avoided by careful graduation of the dose. If "Neo-Salvarsan" preparations are employed, with an initial dose of 0.3 gramme, it is improbable that any serious reaction would take place. In the cases of aneurysm treated at Guy's during the last three years there does not appear to have been any exacerbation of symptoms following treatment with arsenical compounds, even though full doses have been given.

An attempt has been made to follow the progress of patients suffering from aortic aneurysm, who have been under treatment in Guy's Hospital between the years 1919 and 1923 inclusive. The cases are given in tabular form in Table II. The total number of patients is unfortunately small, and only a few of them have received treatment with arsenical compounds. It would therefore be unwise to lay too much stress on favourable results. It has indeed been well recognised that patients with aortic aneurysms may undergo a spontaneous cure, or at any rate enjoy comparatively good health for many years. Thus Osler <sup>8</sup> records a case under his observation, in which an aortic aneurysm was present for over ten years. In the Gordon Museum <sup>9</sup> at Guy's Hospital there are two specimens of healed aortic aneurysms, one affecting the arch and the other the abdominal aorta. On the other hand, the average duration of life in aortic aneurysm was formerly not more than two years, and as a rule once the symptoms became apparent the patient was quite incapable of continuing in any occupation that necessitated manual work.

It may be argued that by the time an aneurysm develops,

irreparable damage to the aortic wall has been done and that no cure can be expected, except from thrombosis of the contents of the aneurysmal cavity. The syphilitic process in the arterial wall is, however, not uniform in its distribution; the very fact of the formation of a saccular aneurysm indicates that the coats of the aorta are specially weakened at one spot. It is therefore quite conceivable that treatment might limit the process as regards the rest of the aorta, and thus prevent further dilatation or the spread of the aortitis to the valves and the entrances of the coronary vessels. Moreover, spirochætes have been demonstrated in the wall of the aneurysmal sac, and these may be killed by anti-syphilitic treatment, thus allowing the yielding wall of the sac to be replaced by firm fibrous scar-tissue.

During the period 1919 to 1923 there are reports of twenty-three cases of aortic aneurysm, who were in-patients at Guy's Hospital, and whom it has been possible to trace since they left hospital. In all of these there was no doubt as to the presence of an aneurysm clinically, and, except in a few cases where it was found at post-mortem examination, the diagnosis was confirmed by an x-ray examination. The Wassermann results make it quite clear that in nearly every case syphilis has been a factor in the disease. In four instances there is no record of the test having been performed, but in the remaining nineteen cases it was positive in all but three (Nos. 4, 7 and 13, Table II). Of these, No. 4 was an aneurysm of the arch, which caused death by rupture; No. 7 was an aneurysm of the abdominal aorta, and No. 13 has a history of two attacks of acute rheumatism and also suffers from nephritis. Unfortunately there is not sufficient evidence in the case reports as to the date of the syphilitic infection to enable any conclusions to be drawn as to the period after infection at which aneurysm is likely to develop. In fact several patients with positive Wassermann reactions were unaware they had ever contracted syphilis.

All the twenty-three were males, but there is one undoubted case of an aneurysm in the ascending aorta and arch in a woman of 47 years of age, who was in Guy's in 1923. Her case has not been included in the present series, as it has not been possible to trace her. Twelve (Nos. 1 to 12) either died in hospital or have been found to have died since their discharge. Of these fatal cases six, or fifty per cent., showed evidence of aortic regurgitation in addition to the aneurysm. In all probability this lesion is an important one in prognosis, as the syphilitic process then involves the aorta in the neighbourhood of the mouths of the coronary vessels and is likely to lead to

their partial occlusion, with resulting fibrosis of the heart muscle.

Reference to Table II shows that of the twelve fatal cases four had received treatment with N.A.B., but in one only 0·45 gramme of the drug was given, as the patient refused further treatment. Case 8 had a prolonged course of injections with a total of 16·2 grammes of N.A.B. After leaving hospital he did well for a time and was able to return to his work as a carter for four months. He then died apparently from acute bronchitis or pneumonia. Cases 9 and 11 both underwent short courses of N.A.B. injections, but in neither case was life prolonged for any considerable time. In case 11 the disease was complicated by tabes dorsalis and a sarcoma of the tonsil. This was removed, but the patient died of septic broncho-pneumonia shortly after the operation.

Eleven cases have been traced and found to be still alive (cases Nos. 13 to 23, Table II). Of these, six had a course of N.A.B. injections, totalling 8 grammes or over in each, four had no N.A.B. treatment, and one only ·75 gramme. Of the last five (Nos. 14, 16, 17, 19, 23), only one (No. 14) has been sufficiently fit to return to work, but he has now relapsed. Of the six who had N.A.B. treatment only one (No. 13) has done badly, and he is the case referred to above with a negative Wassermann reaction and suffering from nephritis in addition to the aneurysm. The remaining five (Nos. 15, 18, 20, 21, 22) have had hardly any symptoms and have been at work since leaving hospital. In four their occupation involves very heavy work. One has been working as an iron-moulder ever since leaving hospital in July 1920, another works in a saw-mill, a third as a bricklayer, and a fourth as a waterside labourer. The five cases successfully treated with N.A.B. have averaged thirty-one months since their treatment in the hospital, so that it would appear that the benefit received has been more than a mere temporary improvement due to rest. Almost all the patients in this series took potassium iodide while in the hospital, and some also did so after discharge.

Unfortunately it has not been possible to see all the patients who have been traced as alive, as some were unable to come for examination. Of the five who have done well after N.A.B. treatment, four have been examined. The x-ray examination demonstrated an aneurysm in all. In one patient, who before treatment had a large pulsating tumour, there was only very slight pulsation of the thoracic wall when he was seen recently.

Although the number of cases here reported as treated with arsenical compounds is small, it must be admitted that the

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results have been very much better than might have been expected. Though it is well recognised that patients suffering from aneurysm may sometimes live a sedentary life for several years, it would be rare to find any who have been able to do ordinary manual labour over periods up to nearly four years, as several of those in the present series have done. In view of the apparently favourable results which have been achieved in the very limited number of cases treated with salvarsan compounds, it is hoped that a more extensive trial will be given to vigorous anti-syphilitic treatment in aortic aneurysm.

In conclusion I wish to thank Sir William Hale-White for his help and advice in the preparation of this paper, and also the physicians of Guy's Hospital for allowing me to refer to the cases under their charge.

TABLE I.—DEATHS FROM ANEURYSM.

(From the Registrar-General's *Statistical Review*, 1921.)

Year.	Total Deaths.		Deaths per Million Living	
	Male.	Female.	Male.	Female.
1906	882	219	53	12
1907	941	199	56	11
1908	867	192	51	11
1909	946	221	55	12
1910	898	225	52	12
1911	935	225	53	12
1912	962	184	55	10
1913	921	234	52	12
1914	902	229	50	12
1915	896	245	52	13
1916	800	202	50	10
1917	770	225	51	11
1918	695	168	46	9
1919	711	180	41	9
1920	782	183	44	9
1921	787	205	44	10



TABLE II.

CASES KNOWN TO HAVE DIED.

Number of case.	Sex and age.	Date of first admission	Duration of symptoms before admission.	Wassermann reaction.	X-ray findings.	Aortic valvular disease.	Anti-syphilitic treatment (Salvarsan and N.A.B.).	Date of death.	Cause of death.	Duration of life after onset of symptoms.	Remarks.
1	M. 57	2.6.19	4 months	+	Fusiform aneurysm.	Regurgitation.	None	11.5.20	Not known	15 months	Refused treatment with N.A.B.
2	M. 54	29.5.19	3 months	+	Aneurysm of arch.	Regurgitation.	.45 N.A.B.	1.7.23		4 years	
3	M. 52	25.8.19	6 months	Not done	Aneurysm of 1st and 2nd parts.	Regurgitation	None	31.8.19	Rupture into bronchus	6 months	
4	M. 56	3.12.20	6 months	Negative	Aneurysm of arch.	None	None	9.12.20	Rupture into bronchus	6 months	
5	M. 33	14.4.20	1 month	Not done	Aneurysm of descending aorta.	None	None	28.4.20	Rupture into oesophagus	2 months	
6	M. 59	29.11.20	8 months	+	Aneurysm of ascending aorta.	None	None	30.11.20	Rupture into pleura	8 months	
7	M. 56	3.3.21	4 months	Negative		None	None	21.4.21		5 months	Aneurysm of abdominal aorta.
8	M. 50	29.3.21	2 years	+	Aneurysm of ascending aorta.	Regurgitation	19 injections of N.A.B., total 16.2 grammes	7.1.22	Bronchitis	3 years	Worked as carman for 4 months after discharge from hospital.
9	M. 57	10.5.21	2 years	+	Fusiform aneurysm.	Regurgitation	5 injections of N.A.B., total 2.5 grammes	7.11.21	Fibroid heart	2½ years	6 weeks work after discharge from hospital.
10	M. 40	31.10.21	1 year	+	Aneurysm of arch.	Regurgitation	None	11.4.22		1½ years	
11	M. 08	21.9.21	4 months	+	Aneurysm of arch.	None	4 injections of N.A.B., total 2.4 grammes	25.11.22	Broncho-pneumonia	6 months	Also suffering from tabes dorsalis and sarcoma of tonsil.
12	M. 45	5.6.19	6 months	+	Aneurysm of ascending aorta.	None	None	November 1920		2 years	No improvement after leaving hospital.

TABLE II (continued).

CASES KNOWN TO BE LIVING.

Number of case.	Sex and age.	Date of first admission.	Duration of symptoms before admission.	Wassermann reaction.	X-ray findings.	Aortic valvular disease.	Anti-syphilitic treatment (Salvarsan and N.A.B.).	Period of observation after onset of symptoms.	Present condition and remarks.
13	M. 31	21.12.20	1 year	Negative	Aneurysm of arch and ascending aorta.	Regurgitation	5 injections, total 3.0 grammes	4 years	History of two attacks of acute rheumatism: nephritis with oedema and ascites.
14	M. 46	18.12.10	4 months	+	Aneurysm of arch.	None	None	4½ years	Light work until August 1923. Since then in bed.
15	M. 40	7.7.20	10 months	+	Aneurysm of ascending aorta.	Regurgitation	Full course of N.A.B.	4 years	Working as iron-moulder ever since discharge. No symptoms.
16	M. 68	31.5.20	3 months	Not done	Aneurysm of arch and descending aorta.	None	None	4 years	Has never been able to work. Markedly dyspnoic. Wassermann negative.
17	M. 66	15.6.23	3 months	Not done	Aneurysm of arch.	None	None	9 months	No improvement. Severe pain.
18	M. 45	5.6.21	2 months	+	Aneurysm of ascending aorta.	None	7 injections N.A.B., total 5.4 grammes	3 years	Has worked in a saw-mill continuously since discharge. No symptoms.
19	M. 61	28.7.21	1½ years	+	Aneurysm of arch.	None	3 injections N.A.B., total 1.75 grammes	4 years	No improvement.
20	M. 47	1.2.22	1 year	+	Aneurysm of arch.	None	8 injections N.A.B., total 3.6 grammes	3 years	Practically no symptoms. Light work in a shop.
21	M. 48	21.2.22	? 8 years	+	Aneurysm of descending aorta.	Regurgitation	5 injections N.A.B., total 3.6 grammes	? 2 years	Well and at work as bricklayer.
22	M. 64	1.6.20	1 month	+	Aneurysm of ascending aorta.	None	6 injections N.A.B., total 3.15 grammes	3½ years	Relapse for one month in 1922. Otherwise health good and at work as a water-side labourer.
23	M. 40	19.5.19	2 years	+	Aneurysm of arch and descending aorta.	None	total 3.15 grammes None	6 years	Never able to work. Marked dyspnoea. Frequent pain.

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## OBSERVATIONS ON THE "TOXÆMIAS" OF PREGNANCY \*

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JOHN LEVER

IN view of certain features that have arisen in the course of the following observations, a tribute is due to the memory of John Charles Weaver Lever, sometime Obstetric Physician to Guy's Hospital, who first discovered the association of albuminuria with eclamptic convulsions.

This remarkable man was born in 1811 and died at the early age of forty-eight. He appears to have been possessed of boundless energy and powers of endurance, both mental and physical; it is recorded that as a student he walked daily for two years from Woolwich to attend nine-o'clock lectures at Guy's, returning again on foot in the evenings. The further quality of common sense added clinical efficiency to his inevitable success—a not invariable combination. According to Wilks and Bettany his consulting-rooms were crowded to overflowing, and for a time he almost monopolised the practice in the southern suburbs of London; it was difficult to find a person of the female sex who had not consulted him. In stressing the prosperity of his private practice it would seem that these authors have failed to attach sufficient credit to the value of his actual work, with which we are the more concerned.

Presumably his crucial discovery was made under the influence of his contemporary, Richard Bright; yet the excellence of his clinical descriptions affords convincing evidence of his unquestionable merits.

Apart from the application of aseptic principles, of which the present-day employment of Cæsarean section is merely an outcome, the science and art of Obstetrics have advanced but little since his time. His various papers, published mainly in the earlier volumes of these *Reports*, are therefore worthy of serious attention.

Of chief interest in the present connection is a report on "Cases of Puerperal Convulsions, with Remarks."<sup>27</sup> To anyone

\* Modified text of a Hunterian Lecture delivered at the Royal College of Surgeons on January 28, 1924.



JOHN CHARLES LEVER, M.D.  
Obstetric Physician to Guy's Hospital, 1842-1859.



who has laboriously surveyed the voluminous and often pseudo-scientific literature of later date, his is a welcome and refreshing account, which graphically conveys the mark of accurate observation. Lever was not obsessed by other than the simplest hypothesis, and indeed it is common to find the obvious rejected most scornfully only by those who are least able to comprehend the complex and obscure. His treatment of eclampsia differed but little in general from the much-vaunted "Dublin method" of to-day, and his results were almost equally successful: if a death apparently due to other causes be excepted, we find that twelve of his thirteen cases recovered.

Wilks and Bettany note with evident disapproval that at the height of his fame Lever "became a *bon vivant*, and ceased to be a teetotaller." To this they tend to attribute his early death, but had they more fully appreciated his colossal output of work they might have formed a kindlier opinion.

#### CURRENT HYPOTHESES

There has been an illogical tendency to group various disorders of pregnancy under one heading, and to attribute their manifestations to a common causal agency. Moreover, it has become customary, by the application of the general term "toxæmia," to convey a false impression of knowledge belied by that very diversity of opinion which characterises our every discussion of these problems. In its literal interpretation the term is innocent enough; but as commonly employed in this particular connection, it almost imparts that comfortable sense of fatalism which is the most insidious enemy to research. As a necessary preliminary to the scientific study of these problems, it is here submitted that any presupposition of a common ætiological factor should be dismissed for the time being, that each form of derangement should be examined strictly on its own merits, and, in certain instances, that each individual case should be regarded as a separate entity.

At the present time there is an inclination to assume that noxious elements or toxins tend to arise directly or indirectly from the ovum, and in particular from its growing edge, the placenta, thereby constituting what one might describe as a form of biochemical neoplasia. Alternatively it is suggested that anaphylactic phenomena are established. Innumerable variations of these theories have been proposed. A different hypothesis has been advanced by Young,<sup>51</sup> who believes that toxins arise from the autolysis of localised areas of placental necrosis, following some form of interference with the maternal blood supply. On first principles one finds this conception

more attractive than those which regard the living tissues of the ovum as a potential source of serious disease. Mackenzie Wallis and Williams<sup>50</sup> suggest that the over-production of a toxic substance in the corpus luteum is the cause of all the trouble.

The Dublin School, whose clinical results are more convincing than their pathological theory in view of the biochemical evidence, appear to imply that additional metabolic products accompanying the pregnant state expose the excretory organs of the body to an extra strain, which is reinforced by the effects of over-eating and defective alimentary elimination;<sup>16</sup> or, as an alternative supposition, that "the food ingested and the toxic elements from the foetus require the same ferments in the blood to neutralise them. The foetal toxin takes some of the elements from the blood which are intended for the digestion of food. This leaves the latter with no ferment, and therefore the food acts as a toxin."<sup>45</sup> In connection with this latter view of the situation, the observations of McQuarrie and Whipple,<sup>32</sup> with regard to the influence of intestinal obstruction on the renal function, are of considerable interest; they attribute the accompanying renal impairment to the action of toxic proteose absorbed from the obstructed gut. An engaging criticism of their work has recently been published by Paramore,<sup>38</sup> who suggests that an increased intra-abdominal tension due to vomiting and other physical factors may be responsible for the kidney defect.

Paramore<sup>39</sup> maintains, on the basis of clinical and experimental evidence, that the intra-abdominal pressure is definitely raised in pregnancy, and that an exaggerated increase of this pressure determines a toxæmia; but he regards this toxæmia as a purely secondary factor, due to mechanical interference with the capillary circulation of the liver and kidneys, and consequent impairment of their excretory functions.

Vitamins and the ductless glands have naturally been held to blame, and there is indeed one aspect of an endocrine disturbance that may be worthy of attention, although at the moment it is purely speculative. Kark<sup>25</sup> has assumed that eclamptic phenomena represent the effects of an over-action of the pituitary gland, which is normally called into play during the later periods of pregnancy for obvious physiological purposes. He suggests that this occasional excess of pituitrin in the system leads to contraction of the arterioles in various parts of the body and produces thereby necrotic foci in the placenta, liver and kidney, and œdema of the brain. It is possible that we may shortly be in a position to test the validity of this



hypothesis by the application of a new and extremely delicate biological test for the detection of pituitrin in the blood.

Quite apart from this potential superabundance of pituitrin it is possible to conceive that a hyperactivity of purposive pressor effects is otherwise induced, whether as a result of circulatory disturbances of reflex or mechanical origin, or under the influence of adrenalin or any of the pressor bases. Unfortunately we have no means of detecting the relative quantities or even the presence of these latter in the general circulation, and for the present we can only hope to observe the vascular phenomena as such.

I contend, however, that we should confine our investigations to the study of tangible physiological, anatomical and pathological factors, rather than that we should allow our minds to make use of an imaginary primary specific toxin for the existence of which there is no direct scientific evidence whatever.

#### BIOCHEMICAL OBSERVATIONS

Of recent years considerable attention has been given to the inorganic constituents of the body under various conditions. This has naturally appealed to those of us who are merely amateur biochemists. Much credit and blame has been attached to the part played by calcium, particularly in the economy of the female. Applying the method of Laidlaw and Payne <sup>26</sup> in determining the total calcium content of the serum in pregnancy, eclampsia, and pregnancy with albuminuria, apart from actual nephritis, I have found no considerable deviation from the normal.

Osman and I <sup>7</sup> investigated the acidosis factor in pregnancy. We found, in common with other observers, a reduction in the bicarbonate content of the plasma. No further reduction was found in cases of albuminuria of pregnancy, although in nephritis proper there is frequently a marked decrease in the alkali reserve, associated with phosphate retention and diminution of the calcium content of the serum. In certain cases of eclampsia, however, a definite fall in the plasma bicarbonate was noted; but I have since attributed this to the effects of the convulsions and of labour itself, as corresponding figures have been obtained in the later stages of labour, and a particularly low figure in a case of pregnancy accompanied by convulsions due to a definite cerebral lesion.<sup>8</sup> It is now generally agreed that the acidosis factor plays a negligible part in the “toxæmias” of pregnancy. Further reference will be made to this subject under the heading of pregnancy vomiting. As

regards what one may term the "physiological acidosis" of pregnancy, Marrack and Boone<sup>33</sup> have demonstrated a primary reduction of CO<sub>2</sub> tension in the blood, and only in a minority of cases an actual alkali deficit, which is presumably due to the excess of base over acid required by the foetus in the later stages of pregnancy.<sup>44</sup> I have been able to detect the characteristic fall in plasma bicarbonate at the earliest stages. It is possible that we may eventually find some relationship between the circulatory changes subsequently suggested and these variations in the acid-base balance. Marrack<sup>34</sup> has further observed that acidosis in nephritis is evidence of a very severe condition, but is not harmful in itself; it does not cause any of the symptoms of uræmia. He also notes in the same paper that renal oedema is not necessarily accompanied by retention of the chlorine ion—a significant point in view of the common teaching. Briggs<sup>4</sup> and others have found no conspicuous deviation of the inorganic elements of the blood in eclampsia.

De Wesselow,<sup>11</sup> who has published excellent work on this subject, aptly observes that the renal lesions of pregnancy can hardly be attributed to the over-straining of a normal function, since the influence of foetal demands in the ordinary course of events appears actually to diminish the quantities in circulation of such metabolites as require excretion. Even in eclampsia there is not that marked accumulation which is found in certain types of nephritis. Farr and Williams<sup>14</sup> found a variable increase in the non-protein nitrogen content of the blood in eclampsia; but this was never really excessive, and the extent of the increase bore no definite relation to the severity of the symptoms. As is elsewhere indicated, the ammonia coefficient fallacy has been satisfactorily exploded, and variations in the nitrogen partition of the urine are no longer regarded as an index of that hepatic disorder which may undoubtedly exist. In fact Nash and Benedict<sup>36</sup> have recently implied that ammonia appearing in the urine is formed by the kidneys and not by the liver. Unfortunately, observations directed to the detection of functional failure on the part of the liver have not hitherto yielded any information of appreciable value.\* Losee and Van

\* Since this lecture was delivered, Comyns Berkeley and E. C. Dodds have presented to the Obstetric and Gynæcological Section of the Royal Society of Medicine, on February 7, 1924, a communication of considerable interest, with particular reference to the detection of hepatic abnormality in eclampsia and the pre-eclamptic state. It may be noted, however, that the biochemical demonstration of hepatic disorder throws little new light on the fundamental pathology of the condition, since it has long been recognised that the liver is definitely affected. From the practical point of view, moreover, it would appear that the tests which they describe assume a positive value at a stage too late in the pre-eclamptic course of events to afford an invariably reliable therapeutic indication.

Slyke,<sup>29</sup> whose observations on the alkali reserve we have already confirmed, found no definite increase in the amino-nitrogen content of the blood or urine in eclamptic women, and conclude that there is no evidence of defect in the desaminating function of the liver. Alsberg<sup>1</sup> found no impairment of lævulose tolerance in eclampsia, and Tallerman<sup>48</sup> has more recently noted a departure from the normal in only one of three cases.

Dienst<sup>12</sup> suggests that thrombus formation is concerned in the pathology of eclampsia—and it is certainly a factor to which we must give attention. He attributes the tendency to thrombosis, for which there is clinical evidence, to an increased blood content of fibrinogen and fibrin ferment in pregnancy; and states that abnormally high levels are reached in eclampsia. To a certain extent de Wesselow<sup>11</sup> supports this observation, but remarks that much higher levels are reached in cases of pregnancy complicated by infection. Falls<sup>13</sup> has demonstrated a slight increase in the coagulability of the blood in pregnancy and especially during labour, but regards the variations as being within normal limits.

On the whole, it must be admitted after due consideration of all the available evidence, that biochemical investigations have hitherto failed to elucidate the fundamental factors of these problems. They have reflected the results of derangement, but they have not thrown light on ætiological antecedents. It must be remembered, however, that our present-day methods are of a somewhat macroscopic order, and that, although the records may be uninspiring, there is every reason to encourage further biochemical research.

Unfortunately biochemistry is a dangerous ally, and those who fly to its aid have often little knowledge of its actual values.

#### ALBUMINURIA OF PREGNANCY

One is inevitably struck by the absence of abnormal features in the average case of albuminuria of pregnancy, with the possible exception of œdema. Although there appears to be only a difference of degree between cases of “symptomless” albuminuria and those which are pre-eclamptic, the former exhibit remarkably little clinical or biochemical deviation from the physiological standard. This was impressed on my attention in the course of investigations on the acidosis factor in normal and abnormal pregnancy.<sup>7</sup> I have further been unable to find any increase in the inorganic phosphate content of the plasma in these cases, such as would afford evidence of renal

retention in that respect. De Wesselow <sup>11</sup> found an almost negligible rise in the blood urea content of mild types of albuminuria, although the urea concentration test showed some slight degree of renal impairment. These and other considerations suggested a comparison with various forms of "functional" albuminuria.

In cases of orthostatic albuminuria apparently due to lordosis, Sonne <sup>46</sup> assumed that the two kidneys would not be equally involved, as the left renal vein would be more liable than the right to compression by an anterior curvature of the spine; and he was able to demonstrate by ureteric catheterisation a left-sided unilateral albuminuria. Rieser <sup>41</sup> postulated a compression of the left renal vein between the aorta and superior mesenteric artery in cases of visceroptosis associated with lordosis. In view of the mechanical conditions obtaining in late pregnancy, an investigation on these lines seemed therefore to be worthy of pursuit.

In each instance the actual catheterisation has been undertaken by Mr. V. E. Lloyd, who has been good enough to collaborate. Hitherto we have unfortunately failed to obtain a sufficient number of suitable cases to afford any satisfactory conclusion. We were, however, encouraged to continue by a definitely positive result in the first case that we examined. Apart from the difficulty of obtaining clinical material, there are various technical difficulties to be encountered. It can easily be imagined that the interior of the bladder may be so distorted in the later stages of pregnancy as to render ureteric catheterisation far from easy; it has been quite impossible to obtain the desired specimens of urine on every occasion, and our results have thus been limited to somewhat pitiable proportions.

Corresponding specimens of urine were obtained from the left and right kidney respectively in five multigravidæ and four primigravidæ. The former showed no marked difference in the protein content of the urine from either side. Although there was slightly more on the left than on the right in certain cases, and in no case was this position reversed, the differences were regarded as being within the limits of experimental error. The relative quantities of urine varied considerably, but the variation was not uniform. In none of these cases was there excessive albuminuria. In three of the four *primigravidæ*, however, a definitely asymmetrical excretion of protein was observed. In the first case, a heavy cloud on the left and a faint trace on the right; in the second case, 20 parts per thousand on the left, and 6 parts per thousand on the right; and in the third case, of which details have already been published,<sup>9</sup>

14 parts per thousand on the left and 1·2 parts per thousand on the right. The fourth case showed only 0·4 part per thousand on either side. There was very little difference in the relative quantities of urine obtained from either ureter over a corresponding period in any of these latter cases. It will be noted that in no case of the whole series was the urine of the right kidney completely free from protein.

In spite of general opinion as expressed in recent years, we are able to suggest, therefore, that mechanical pressure and a resulting hyperæmia of the left kidney exercise a certain ætiological influence. At the same time it is indicated by the above observations that this particular factor does not represent the whole matter, since albuminuria was invariably found on the right side in some degree. Rather than attempt to support these experimental data with indirect evidence, which is always so fatally plentiful, we shall propose to continue the investigations as opportunity occurs and await definite results. In the meantime it may be profitable to examine other possible circulatory alterations with further lines of research in view. For the moment toxic influences will be left out of account; although it must inevitably be borne in mind that these may play a major part, and it is also agreed that the ultimate effects of vascular changes are immediately due to ill nutrition of the tissues and the possible production of secondary toxic agencies.

The pregnant uterus may effect local venous compression, of which we have already suggested one particular instance; \* it may also determine an increase in intra-abdominal pressure, as Paramore<sup>39</sup> maintains. These influences may be further reinforced by a general augmentation of venous pressure such as would accompany the efforts of labour, vomiting in late pregnancy, convulsions from whatever cause, and even the straining due to constipation. The local pressure effects may be exerted on the vena cava itself or on its branches; further instances are to be found in the varicose veins, hæmorrhoids, discoloration of the vulva, and œdema of the lower limbs (apart from renal defect) which commonly accompany pregnancy. It is tempting to postulate, in association with the implied compression of the left renal vein, a circulatory disturbance of the corresponding supra-renal gland, which might explain certain features of eclampsia itself; but, until we have a means of estimating the adrenalin content of the blood, this conjecture

\* Lever believed that "the gravid condition of the uterus, by its pressure, prevents the return of the blood through the emulgent veins; and hence is the cause of the renal congestion, and the consequent albuminous condition of the urine." <sup>27</sup>

represents the wildest speculation. Paramore<sup>39</sup> believes that an increased intra-abdominal pressure directly determines an occlusion of the *capillaries* in the liver and kidney; though this is a proposition which one will leave him to support. It is well recognised that albuminuria frequently accompanies the later stages of labour: reference will be made to a case in which albuminuria was apparently secondary to the efforts of continued vomiting towards the end of pregnancy; and details have been published of a case in which a marked transient albuminuria immediately followed the incidence of convulsions due to a definite cerebral lesion in a pregnant woman near term.<sup>8</sup> Albuminuria is indeed not infrequently found after epileptic attacks, and in tetanus and apoplexy, quite apart from pregnancy. Fischl<sup>15</sup> was able to produce in animals not only albuminuria but also an actual nephritis by repeated experimental lordosis. Russell<sup>42</sup> freely admits the importance of the mechanical or anatomical factor which leads to circulatory stasis in the kidney and determines the actual onset of the albuminuria in orthostatic cases, but at the same time he postulates the co-operation of additional elements. In all probability this consideration applies with even greater force to the albuminurias of pregnancy.

Another important series of possibilities is suggested by the observations of Pembrey<sup>31</sup> and his fellow-workers on the albuminuria which accompanies muscular exercise. This condition is not apparently due to the action of metabolic products, as it is not a marked feature of prolonged periods of muscular work.<sup>10</sup> It was originally attributed to venous congestion due to relative cardiac incompetence. Pembrey and his collaborators, however, found the albuminuria to be preceded by oliguria or anuria, which they believe to represent in turn a purposive renal vaso-constriction. Although the average case of albuminuria of pregnancy is not accompanied by any marked decrease in the output of urine, the more serious cases and the aberrant types mentioned above are commonly characterised by oliguria. Even in the orthostatic variety, Russell<sup>42</sup> and others have noted that a high degree of albuminuria is invariably associated with a scanty excretion of urine. In labour we may reasonably expect to find an adjustment similar to that observed in other forms of muscular activity. In pregnancy there are at least two possible factors which might conceivably determine a compensatory vaso-constriction in various parts of the body, including the kidneys and liver: one is a physiological increase in the capacity of the vascular system; another is the increased capacity due to venous obstruction, which has been demon-

strated in Bolton's<sup>2</sup> well-known observations on the effects of experimental narrowing of the inferior vena cava.

These and other reflections afford a sufficient indication to re-survey the circulatory conditions as they exist in the pregnant woman. One obvious field of inquiry is provided by a comparison of the vascular features obtaining in quadrupeds, where certain direct pressure effects are presumably eliminated. Few relevant observations seem to have been made on the pregnant animal. "Franck asserts the appearance of a pregnancy albuminuria in cows and mares six to eight weeks before parturition. Other authors, however, obtained negative findings in such instances. Simader, on the other hand, observed albuminuria regularly in connection with parturition in cows, the contents in albumin being the greatest in primiparæ." \* The term "eclampsia" is so differently applied in veterinary science as to render comparison of human conditions almost impossible until we reach a better understanding.

(It is hardly necessary to note that albuminuria associated with pregnancy and due to antecedent nephritis has been eliminated from the above considerations.)

#### ECLAMPSIA

According to the point of view, eclampsia presents a pathological problem of unlimited interest or a train of truly terrifying symptoms. Its most impressive features are the cerebral manifestations and the high blood pressure with which they are commonly associated. The accompanying renal lesions have inevitably suggested a comparison with uræmia, which unfortunately affords us little help. There is even greater variation between different cases of uræmia than there is between different cases of eclampsia. Moreover, as Batty Shaw<sup>43</sup> has pointed out, the term "uræmia" itself is a misnomer; though useful clinically, it implies a state of affairs that is unsupported by experimental evidence. Marrack<sup>35</sup> has justly observed that the disturbances usually classed as uræmic are not necessarily allied with evidence of renal retention or of acidosis. Such disturbances are frequently found in patients with high blood pressure but with fair renal efficiency. On the other hand, none of the characteristic symptoms may be exhibited in cases with extreme degrees of renal impairment.

It is in general with the former of these types that eclampsia may be appropriately compared, although eclamptic convulsions are occasionally unaccompanied by any marked increase of

\* Quoted from Hutyra and Marek.<sup>24</sup>

blood pressure, and although on *cursor*y examination the kidney may show striking evidence of defect. In spite of oliguria and excessive albuminuria, evidence of a serious accumulation of waste products in the blood has not been forthcoming as a rule, though it is true that certain of these products might easily have escaped the biochemist's eye.

To attribute all forms of eclampsia to a uniform sequence of pathological events is almost as unreasonable as to apply a common cause to all the ills of pregnancy, and doubtless the renal element assumes a paramount importance in various cases; but it must be admitted that in the majority it would appear to play a secondary part. Certainly brilliant results have been recorded from decapsulation of the kidney in apparently hopeless cases,<sup>37</sup> and it would be absurd to suggest that the renal influence may not predominate; but for the moment we are groping for fundamental ætiological factors rather than portraying the manifestations of disease.

Post-mortem and clinical appearances imply a definite derangement of hepatic function. I understand there is corresponding biochemical evidence, but that already published is not convincing; and, even were the fact established, it would not necessarily indicate the source of trouble. It is obvious that any satisfactory hypothesis must take into account the liver lesions; and it may be said at once that these are not such as could be explained on the basis of passive venous congestion via the hepatic vein. The influence of toxic bodies in the portal or general circulation, capillary occlusion as suggested by Paramore,<sup>39</sup> or impairment of the afferent blood supply however induced, are all potential factors, though each is highly speculative: the liver does not readily reveal its secrets. As to whether the hæmorrhages precede the necrosis or the necrosis the hæmorrhages, one certainly does not feel competent to express an opinion. The latter view appears to be commonly accepted by histologists.

It is easy enough to explain the cerebral symptoms and post-mortem findings in the brain on grounds of circulatory disturbances if we consider the possible effects of hæmorrhages, thromboses, congestion and œdema. The excellent results of veratrone administration recorded by Stevens<sup>47</sup> and others have afforded striking evidence of the beneficial influence of lowering the blood pressure in cases exhibiting eclamptic convulsions; and the occasional good effects of venesection cannot seriously be attributed to the removal of toxins from the circulation. The *causes* of hyperpiesis have already been discussed; but, at the risk of repetition, it is again suggested that



we should to some extent concentrate our attention on the vascular factors of this grave disorder. I have under investigation at the present time a family of the "arterio-sclerotic kidney" type in which the obstetric histories are of great interest; the incidence of eclampsia is marked. It is always conceivable that even a clinical study of such associations may afford some clue towards the solution of the problem.

All theories have been necessarily strained to meet the conditions presented by post-partum eclampsia. Through the courtesy of Dr. G. D. Eccles, I have recently been able to examine one of these cases, and found the following features of interest. The pregnancy was apparently quite normal, although the urine had not, unfortunately, been examined previously, and the child (the second) was born spontaneously and uneventfully at eight o'clock one morning. At 11 p.m. on the same day, the first fit followed a short period of headache and vomiting. The patient was then admitted to hospital and had two further fits during the night. On the following day, when I saw her, she was comatose, with stertorous breathing and cyanosis; systolic blood pressure 168; bilateral extensor plantar reflex; no œdema; marked oliguria and albuminuria. In spite of the latter, the plasma bicarbonate was  $\cdot 0273$  (molar concentration), and the blood urea 45 mg. per 100 c.c.; the inorganic phosphate content of the plasma was 4.5 mg. per 100 c.c.; and even this slight increase was presumably due in part to the fact that one was unable to centrifugalise the blood immediately after collection. These figures show no marked deviation from the normal. She died three days later without regaining consciousness; but a post-mortem examination was not allowed. This is an incomplete study of a single case; but one could not fail to be impressed by the clinical picture of an essentially cerebral lesion and the absence of evidence of serious renal retention. I make no apology for inserting this abbreviated account. The accurate and detailed record of actual cases is, in the present state of our knowledge, worth a host of theories; and I would beg to commend as an example a report recently published by Bradshaw.<sup>3</sup>

#### "ACCIDENTAL" ANTE-PARTUM HÆMORRHAGE

Hæmorrhages of this class are not customarily designated as "toxæmic." Although the ætiology implied may ultimately prove to be correct, the present-day use of the term suggests a somewhat unjustifiable idea of superior information. Fortunately the treatment of the condition rests on a sound basis

provided by general experience. It is due to remark on the excellence of the clinical and pathological records published a few years ago by the late Gordon Ley.<sup>28</sup> Whatever the future may decide as to the validity of his conclusions, the merits of his actual observations will inevitably withstand the test of time. Admittedly this form of hæmorrhage is frequently associated with albuminuria, and occasionally with eclampsia; but it is surely illogical to postulate *ipso facto* a common ætiological agency. It is indeed obvious that in the large majority of cases the albuminuria is not discovered until the hæmorrhage is manifest, although it may have pre-existed. I have in mind certain instances, in which the albuminuria definitely followed the hæmorrhage in point of time and I am equally aware that a reverse order of events may obtain. Systematic ante-natal supervision will determine the common sequence, but this unfortunately will not prove anything. The histological appearances of the affected uterus have not been similarly interpreted by different observers. Although Gordon Ley and others have regarded the œdema, necrosis and hæmorrhage as being due to a common cause (toxæmia), and remarked that the hæmorrhages were in fact secondary to the necrosis, it has been alternatively contended that the necrosis is secondary to the hæmorrhage.

Young<sup>51</sup> has argued that the underlying and primary element is an interference with the maternal blood supply; this may be due to simple mechanical factors determining a separation of the placenta from the uterine wall, or to a blockage of the ovarian or uterine veins from thrombosis, kinking, direct pressure, etc. Without taking into consideration for the moment the further stage of his hypothesis, which attributes any accompanying "toxæmic" symptoms to the autolytic products of secondary placental infarcts, I again submit that potential mechanical and vascular factors should be seriously examined. If we reflect on the anatomical relationships of the pelvic and abdominal veins in late pregnancy, the local and general changes in pressure, the possibility of vaso-motor disturbance and that of any increased coagulability of the blood, we shall find a sufficient field for research, without the necessity of postulating a "hidden hand." With a growing tendency to apply Cæsarean section to the more serious cases of antepartum hæmorrhage, our opportunities of direct observation are increasing. I recently performed this operation on a severe case of "accidental" hæmorrhage, chiefly "concealed," partly "revealed," and the localised distribution of the lesions was very evident. There was a large retroplacental clot and the foetus had apparently been dead for some hours. The uterine muscle

in general was not apparently necrotic, and contracted with fair rapidity after removal of the intra-uterine contents. There had been a very considerable effusion of blood between the layers of the left broad ligament, and the corresponding ovarian vein was thrombosed; this effusion had spread at any rate into the subperitoneal layer of the uterine wall adjoining, but there was no evidence of hæmorrhage elsewhere. Incidentally this patient had had fourteen previous pregnancies; her abdominal wall was particularly lax, and the urine contained albumin (first discovered after the onset of hæmorrhage)—all of which are relevant points. Young has compared the appearances in similar cases to those produced by a sudden strangulation of the ovarian veins in the axial rotation of ovarian cysts; and certainly the aptness of this comparison has been obvious on several occasions in my own experience.

As regards the relationship of the albuminuria, etc., to the hæmorrhage, I am not prepared to press any particular hypothesis. The common ætiological factor suggested by Gordon Ley and others of the same opinion would certainly afford a reasonable explanation were it substantiated in fact, although it is exceptional to find toxæmic symptoms associated with hæmorrhages in the earlier months of pregnancy. Young and Miller <sup>52</sup> have adduced as additional evidence in favour of their theory, a series of cases of placenta prævia accompanied by albuminuria and even eclampsia; whereas Haffner,<sup>18</sup> after an extensive and careful study, has concluded that there is no direct relationship between albuminuria and placental infarction. Paramore <sup>40</sup> maintains that the increased volume of the uterus due to “ concealed ” hæmorrhage so adds to the already raised intra-abdominal pressure as to affect directly the functions of the liver and kidneys. One objection to this contention is the undoubted association of “ accidental ” ante-partum hæmorrhage with multiparity, as in the case outlined above, where the laxity of the abdominal wall was particularly noted. To say the least, consensus of opinion is not striking; and since the satisfactory nature of the treatment does not demand any special urgency, it behoves us deliberately and without bias to accumulate definite facts before proceeding to further speculation.

#### VOMITING OF PREGNANCY

Although no completely satisfactory explanation has hitherto been afforded to account for the milder degrees of nausea and vomiting which so commonly characterise the

earlier period of pregnancy, the work of recent years has gone far to elucidate the pathology of those more serious forms of vomiting which have been variously termed "pernicious" or "toxæmic." The former of these expressions is non-committal; but the term "toxæmic" would appear to be especially misleading in this connection, as every biochemical and histological manifestation scientifically observed can be attributed to the effects of the vomiting itself. I need not review in detail the admirable work of Harding<sup>19</sup> on this subject nor the psychological theory of persistent vomiting in pregnancy expounded by Hurst,<sup>20</sup> since these are already well known; but I may be allowed to recount in brief certain observations of my own, although the results are of a negative character.

The work of others, to which further reference will be made, had led one to assume for the time being that the more serious degrees of this condition were due in general to the starvation and dehydration consequent upon the vomiting and lessened intake; at the same time one had been satisfied by certain definite clinical observations that the ordinary degrees of "morning sickness" or "physiological" vomiting were not entirely attributable to a hysterical factor. The object was therefore to investigate the latter type of case from a biochemical point of view. To provide a working basis several factors were taken into consideration. Harding had noted in his earlier papers evidence of ketosis occurring in the mildest cases of nausea, which he attributed to carbohydrate depletion; a lowering of the alkali reserve had been demonstrated even in early pregnancy; and a marked increase in the ammonia acid ratio had been shown in the urine of more serious cases of pregnancy vomiting. It was suggested that this might imply a shortage of phosphate available for "buffering" purposes.

In the first place one found that the bicarbonate content of the plasma was not appreciably reduced below the normal pregnancy value, even in cases of moderate severity. This confirms the observations of Losee and Van Slyke<sup>21</sup> in the same direction. It must be remembered, however, that in cases of actual vomiting acid is being eliminated via the stomach; this may account to some extent for the adjustment of acid-base balance. No evidence was found of any reduction in the blood sugar content; little importance was attached to this observation as the level tends to be maintained even in extreme starvation. As regards the phosphates (which I estimated by Briggs'<sup>5</sup> modification of the Bell Doisy method) it was soon obvious that the inorganic phosphate content of the plasma showed no evidence of depletion: the average figure obtained

in cases of vomiting of mild and moderate degree was 8.2 mg. phosphorus per 100 c.c. (range 2.85 to 4.0). These values may be compared with those obtained by de Wesselow<sup>11</sup> in normal pregnancy and in non-pregnant females. It was further considered, however, that the inorganic phosphate content of the plasma, as in the case of blood sugar, might not justly reflect the phosphorus reserves of the body in general. There are theoretical and particularly practical objections to determinations of a metabolic balance which led one to estimate instead the "acid soluble" phosphorus content of the blood corpuscles. For technical reasons, this procedure necessitates estimations of the "acid soluble" phosphorus content of whole blood and that of its corresponding plasma respectively, together with hæmatocrit readings in each individual case. The necessary observations and calculations having been made, one again found no evidence of depletion. The average figure obtained in cases of mild and moderate vomiting was 80.6 mg. phosphorus per 100 c.c. corpuscles, compared with 29.9 in normal non-pregnant females. (It may perhaps be explained that "acid soluble" phosphorus includes the phosphorus of inorganic phosphates together with that of organic substances other than lipoids. The organic factor appears to be contained in the corpuscles, whilst the plasma phosphate is almost entirely inorganic.) The excretion of phosphate during twenty-four hours in a few of the cases under consideration showed no increase; nor was any direct evidence obtained of excessive elimination of acid in the urine. It was further observed that the ammonia acid ratio showed no definite deviation from the normal—and here I must again remind you that I was investigating cases of only comparatively mild degree. Finally it became obvious that there was no excretion of "acetone" bodies in the large majority of these cases. Harding agrees with me that his earlier observations were at fault in this respect.<sup>20</sup>

It is not without interest to note, as indicating the unreliability of unsupported clinical and therapeutic observations, that pending the results of the above investigation I treated a very large number of cases of pregnancy vomiting at an antenatal clinic and elsewhere by administering basic sodium phosphate, in the form of *Sodii phosphas effervescens*, with confidence and with remarkably good results. As these were almost invariably cases of persistent vomiting continuing beyond the fifth month of pregnancy, one can only believe that they afforded further evidence of cure by suggestion! The metabolism of phosphorus in pregnancy naturally presents a much more intricate problem than one might appear to have indicated,

and negative evidence cannot be conclusive; at the same time there appears to be no indication to proceed further along these particular lines. It remains to consider for a moment the ætiology of the ordinary phenomenon of "morning sickness," and to proceed to an examination of the evidence relating to the more serious conditions of persistent and pernicious vomiting. To explain the former, Harding <sup>19</sup> postulated a carbohydrate disturbance occurring in the maternal liver as the primary factor. This derangement of the ketogenic anti-ketogenic balance essentially depends on a shortage of glycogen, due in turn to foetal demands unsatisfied by a sufficiently increased maternal intake, and leads to the production of acetone bodies in the blood and urine. Lochhead and Cramer <sup>30</sup> have shown that the presence of the foetus imposes a special demand for carbohydrate and that the pregnant woman has therefore a tendency to pass into a state of specific carbohydrate starvation. But whilst it is freely admitted that these factors assume the utmost importance in continued vomiting, a failure to demonstrate ketosis in the early stages inevitably implies that they are not a primary cause. In fact we have at the present time, so far as I am aware, no real evidence of biochemical abnormality at the outset of the condition; and still less have we any evidence whatsoever to indicate a specific "toxin." Dr. Hurst has suggested that the "physiological" degrees of nausea and vomiting are reflex in origin, and that the pathological perpetuation and accentuation of the condition are primarily hysterical, the result of auto- and hetero-suggestion. These hypotheses are obviously open to doubt if it can be shown that any biochemical deviation from the normal precedes the vomiting, and if any of the manifestations cannot be explained as a result of the vomiting with its consequent starvation and dehydration. Reference has already been made to the misinterpretation of changes in the nitrogen partition of the urine; as a result of persistent vomiting, we have on the one hand a diminished intake of nitrogen, and on the other a ketosis, which together can sufficiently account for the high "ammonia coefficients" observed. Underhill and Rand <sup>49</sup> showed that it was possible to ascribe all such changes in pernicious vomiting to starvation, and that the administration of carbohydrate tended to re-establish the normal value. Certainly Gilliat and Kennaway <sup>17</sup> considered starvation alone to afford an inadequate explanation of the intensity of the changes; but it must be remembered that the disturbance is not so severe as to cause any marked alteration in the acid base equilibrium. The further data of Harding and Potter <sup>21</sup> are in conformity with the latter

observation; they found that, although the excretion of “ acetone ” bodies in the urine might reach a remarkably high level, their concentration in the blood was not excessive, and not to be compared with that in such cases of diabetes as show a marked depletion of the alkali reserve; nor was the alveolar  $\text{CO}_2$  generally lowered.

In severe cases an increase in the non-protein nitrogen and uric acid of the blood has been noted. Harding and Drew <sup>22</sup> believe that this is due to the dehydration following continued vomiting, and to an impairment of renal function resulting from the lack of available water. When the anhydræmia and oliguria had been overcome by therapeutic reinforcement of fluids, a reduction of the blood constituents in question was found to accompany the diuresis. Added to the ill effects of carbohydrate starvation in progressive vomiting we must therefore consider the influence of dehydration and its consequences.

As regards the renal impairment, however, we must take into account the further possibility of a mechanical factor on the lines suggested by Paramore. Assuming for the moment that a mechanical or purely vascular factor may determine renal defect in pregnancy, we must admit that violent vomiting would very definitely accentuate its operation, especially in the later stages. I recently had an opportunity of investigating a patient whose features admit of some such explanation. She was admitted to hospital as a case of albuminuria of pregnancy (“ toxæmia ” implied). On being asked to see her, I found that she was a case I had previously examined at the ante-natal centre on several occasions; she had always been “ full of symptoms ” without apparent organic basis. She had albuminuria on admission and had been vomiting vigorously for four days; full term was nearly due. Examination of the blood showed a plasma bicarbonate value of  $\cdot 0280$  and an inorganic phosphate content of  $3\cdot 4$ —approximately normal figures affording no evidence of renal retention. A twenty-four-hours specimen of urine showed oliguria, marked acetonuria, and albuminuria. On her being persuaded to eat and drink without vomiting, the patient’s condition rapidly returned to normal, and she was shortly delivered of a live child without further incident. Albuminuria recurred during labour but disappeared entirely two days later.

There is no reason to believe that every instance of vomiting in pregnancy is attributable to a common cause; the bulk of the evidence is to the contrary. But I do urge that we have at the present time no definite indication of a primary toxæmia,

and that, generally speaking, the treatment is most emphatically *not* further starvation.

The nature of my argument precludes a summary of conclusions. If I have suggested anything, it is that we should regard individual cases without preconceived diagnosis or theory and continue to investigate them with every means at our disposal; that we should accurately record our observations without premature inductive comment; that we should reconsider and further examine the vascular conditions of pregnancy in general and in detail; and that we should not proclaim the existence and influence of toxic agencies until they have actually been demonstrated.

Without being given to undue optimism in these matters, I do feel that the problem of pernicious vomiting has for practical purposes been solved. As regards albuminuria and eclampsia, therapeutic indications still rest largely on a basis of clinical values. My own experience is much too small to enable me to add anything of value to the opinion expressed at the British Congress of Obstetrics and Gynæcology in 1922, to the reports of which I refer you without prejudice. At the same time I would prefer in the present state of our knowledge to treat a given case on its own merits, rather than in accordance with any prearranged plan, however distinguished its origin. There are very definite objections to the grouping of cases for statistical purposes: not only is it a questionable procedure to subordinate treatment to research; but it is also extremely doubtful whether statistical methods are of any considerable value in elucidating problems that comprise such a multiplicity of elements.

I have already apologised for the poverty of my experimental data. For this I do not entirely accept the blame. In the first place, anyone who has engaged in combined clinical and biochemical research on cases for whose treatment he may have also been responsible will fully realise the difficulties. Team work is essential in medical research. By "team" one does not imply a committee of individuals similarly qualified, however highly. The various laboratory methods and the therapeutic technique of the present day each require a special degree of skill and training; and it is almost impossible for any ordinary person to combine efficiency in both respects with the requisite exercise of clinical insight and judgment. At all events the attempt involves an unnecessary expenditure of time and energy.

Secondly, I would refer to the very considerable difficulty that has been experienced in obtaining clinical material, and



accommodation for cases under investigation. Every available facility has been given by the staff of my own hospital, and I am grateful to others for the occasional opportunity of making observations. But, as Janet Campbell <sup>6</sup> has emphasised, the limited numbers of obstetric beds in our hospitals afford entirely insufficient scope for teaching purposes; much less is there provision for research. Perhaps it would ultimately lead to a better organisation if we clearly and candidly exposed the gaps in our knowledge, and at the same time made evident the hopefulness of our task.

My thanks are due to Mr. Bellingham Smith and Mr. Harold Chapple, who have allowed me to investigate cases under their care. To Dr. J. H. Ryffel I am particularly indebted for laboratory facilities; both he and Dr. W. W. Payne have repeatedly and willingly advised me with regard to biochemical procedures.

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## MEGALOCYTIC AND NON-MEGALOCYTIC ANÆMIAS

By A. C. HAMPSON, B.A., and J. W. SHACKLE, B.A.

IN an examination of the blood in twenty cases of Addison's anæmia and ten cases of anæmia following hæmorrhage, Price-Jones <sup>1</sup> showed that the mean diameter of the red cells in Addison's anæmia is greater than the mean diameter of the red cells in healthy persons; whereas in anæmia following hæmorrhage the mean diameter is smaller than the mean diameter of the red cells in healthy persons.

The remarks in this paper are founded on an investigation of 150 cases of anæmia. Of these, thirty were cases of Addison's anæmia, and twelve were cases of sprue; the remainder occurred in other conditions, which will be discussed in Part II of this paper.

According to the most usual classification, anæmias are divided into two groups—primary and secondary. This classification is obviously unsatisfactory. Many cases of septic anæmia are described as secondary, although no organism may have been isolated. Addison's anæmia, on the other hand, is classed as primary, although there is growing evidence as to its toxic nature. In most of the cases of Addison's anæmia in this series, a hæmolytic *Streptococcus longus* was isolated by Dr. F. A. Knott from the duodenum; and in a number of these cases there was a definite reaction on extraction of infected teeth or enucleation of septic tonsils, a distinct fall in hæmoglobin taking place.

A more rational classification of blood diseases would appear to be one based on the blood condition. Ehrlich and Lazarus <sup>2</sup> suggested a classification into megaloblastic and non-megaloblastic anæmias. Hunter <sup>3</sup> objected to this on the basis that megaloblasts were inconstant in Addison's anæmia, and that, on the other hand, they occur in other anæmias. Many of the cases of Addison's anæmia included in the present series have been thoroughly investigated at short intervals, many films being examined on each occasion. Our observations confirm Hunter's contention, the appearance of megaloblasts occurring frequently in definite crises, no megaloblasts being found in the intervals. On the other hand, numerous megalocytes have

invariably been present—often forming almost the only cells (see Figs. 1 and 2).

### *Technique*

For the measurement of cells a standard technique was employed. Dry films were stained with Jenner's stain, and intensified with 1 per cent. aqueous solution of eosin, as employed by Price-Jones.<sup>1</sup> Each of 500 consecutive cells was measured in two diameters at a magnification of 3,000 diameters, the

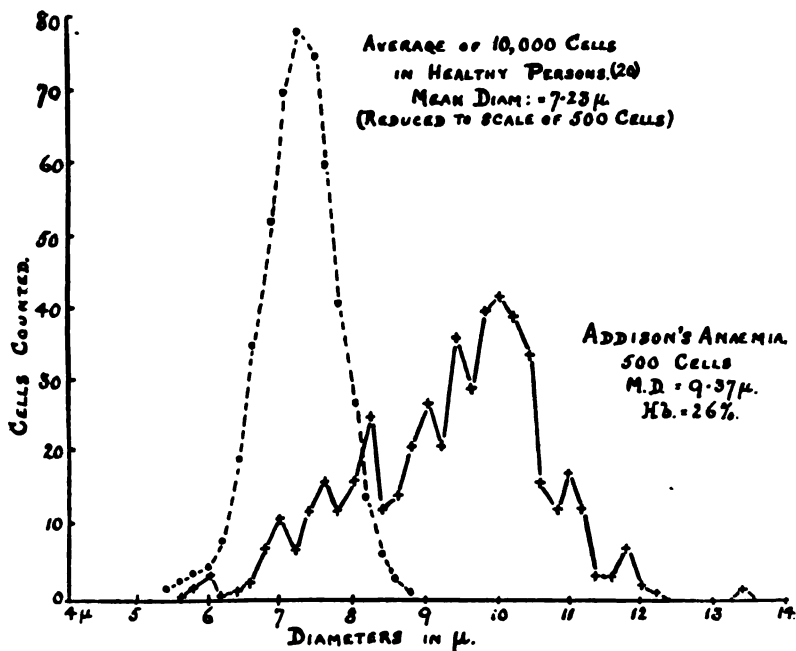


FIG. 1.

A case of Addison's anaemia showing megalocytic cells.

average of the two diameters being taken. A curve was then plotted, showing the number of cells of each size found. It should be noted, therefore, that as 500 cells were measured in each case, the abscissæ bear no relation to the number of cells per c.mm. (In Fig. 8, however, the abscissæ represent absolute numbers of cells per c.mm.)

For comparison, a curve representing the average cell-distribution in a normal healthy person has been superimposed. This has been obtained by measuring 500 cells in each of twenty individuals, and reducing the compounded curve so obtained to a scale of 500 cells.

It should be noted that, as Price-Jones pointed out, a few megalocytes may be present in hæmorrhage anæmia, and we have found such cells constantly present in other "secondary"

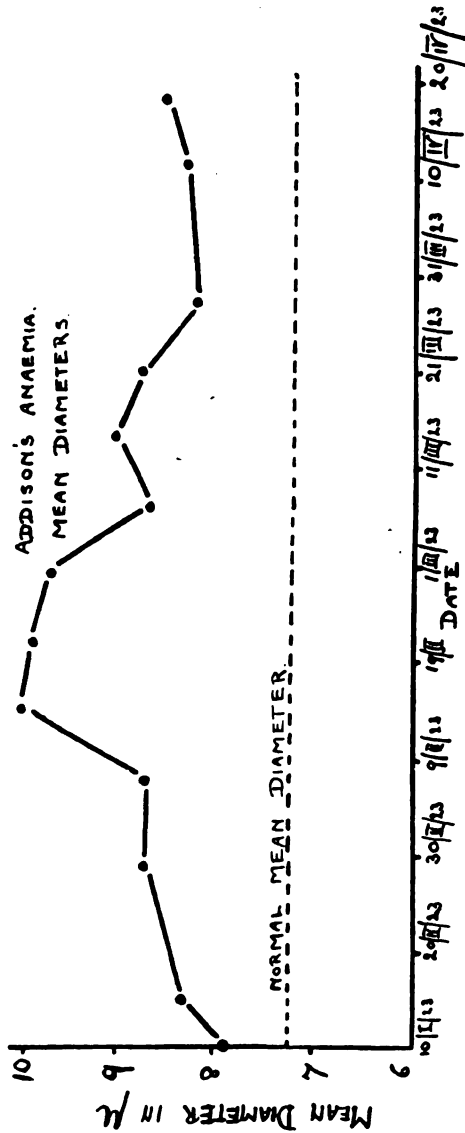


FIG. 2.

Curve showing variation in mean diameter in a case of Addison's anaemia.

anæmias. No confusion should arise, however, between these two conditions. As is illustrated in Fig. 3, in secondary anæmias the majority of the cells are normocytes.

The difference between the two types is, of course, clearly shown by a comparison of the mean diameters. The cell

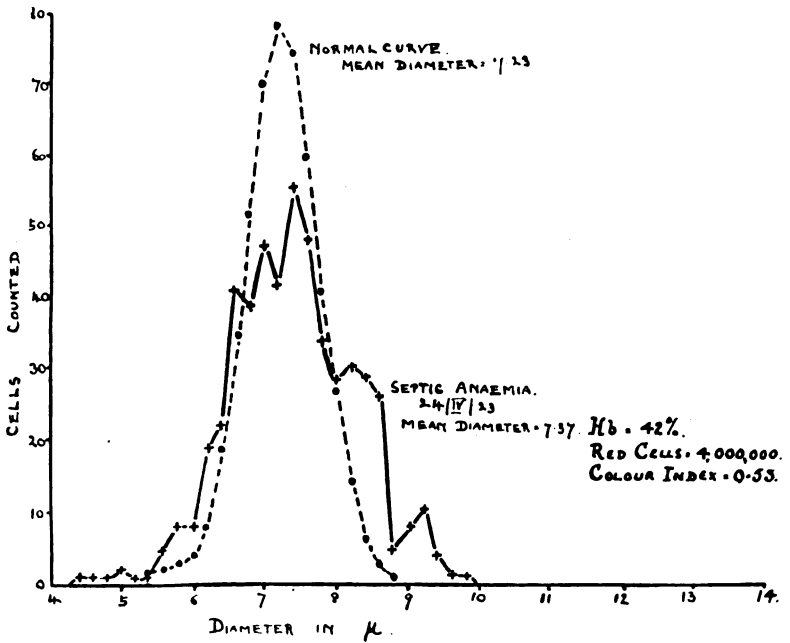


FIG. 3.

A case of septic anaemia.

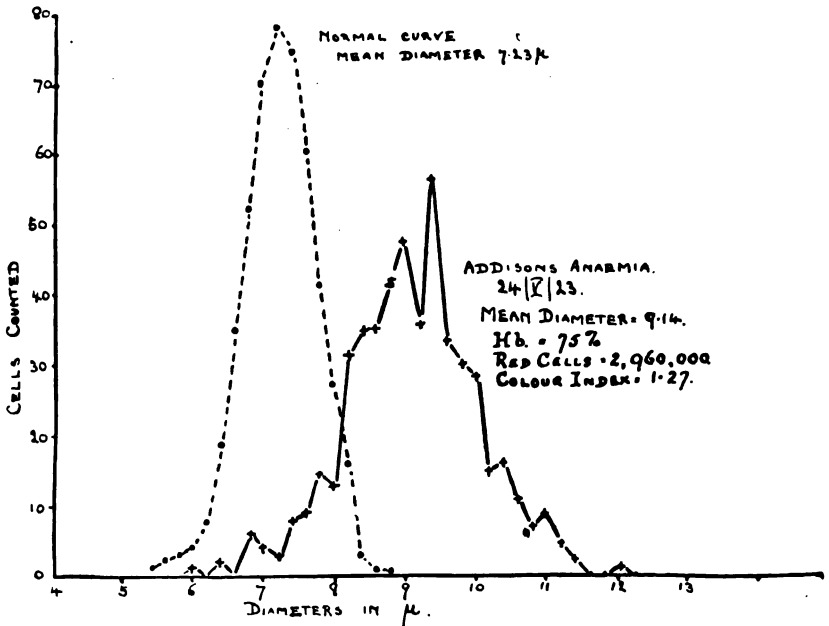


FIG. 4.

A case of persistent diarrhoea shown to be Addison's anaemia.

distribution curves in these anæmias are, moreover, more symmetrical.

These investigations suggest a classification of anæmias into megalocytic and non-megalocytic, the former including Addison's anæmia, sprue, and bothrioccephalus anæmia.

## PART I

### MEGALOCYTIC ANÆMIAS

In all the cases included in this series, a diagnosis had either been made before cell-measurement, or was fully confirmed by the later clinical course of the disease.

#### (A) ADDISON'S ANÆMIA

Patients suffering from Addison's anæmia often present themselves for treatment of symptoms other than those directly attributable to the anæmia:—thus patients often come under observation for intractable diarrhœa, or for buccal ulceration. Intractable diarrhœa has been shown to be associated in many cases with achlorhydria, and should always give rise to a suspicion of the possibility of Addison's anæmia, for which condition a thorough investigation of the blood should be carried out, even if the hæmoglobin has been shown to be normal.

*Case 1.—A case of persistent diarrhœa shown to be Addison's anæmia.*—C. G., male, æt. 67, gave a history of persistent diarrhœa during the last three years. On examination, the tongue was clean but fissured. Blood examination showed hæmoglobin 75 per cent., red cells 2,960,000 per c.mm., colour index 1.27, white cells 2,800 per c.mm.—polymorphs. 49 per cent., lymphocytes 45 per cent., eosinophils 1 per cent., hyalines 5 per cent. There was some poikilocytosis. Several cells showed polychromasia and punctate basophilia. Considerable numbers of megaloblasts were seen. The cell distribution curve is shown in Fig. 4. Van den Bergh's test showed a positive indirect reaction. A fractional test-meal showed complete achlorhydria.

Hunter attaches great importance to buccal ulceration in the diagnosis of Addison's anæmia. Buccal ulceration, however, occurred in not more than half of the thirty cases in this series; and, on the other hand, was present in a number of cases of other anæmias, as in a case of streptococcal septicæmia following removal of tonsils. Dr. G. Marshall has found cases of buccal ulceration in otherwise uncomplicated achlorhydria. Buccal ulceration, however, should always call for careful investigation.

One of the cases in this series (Case No. 9, Table I) came up to Out-patients complaining of this alone.

About 80 per cent. of cases of Addison's anæmia show definite signs of spinal cord disease, indistinguishable from subacute combined degeneration of the cord, and in almost every case of subacute combined degeneration, anæmia develops sooner or later (Hurst <sup>4</sup>). In the cases which we have examined, this anæmia has always been of the megalocytic type, indistinguishable from Addison's anæmia. Similar changes were

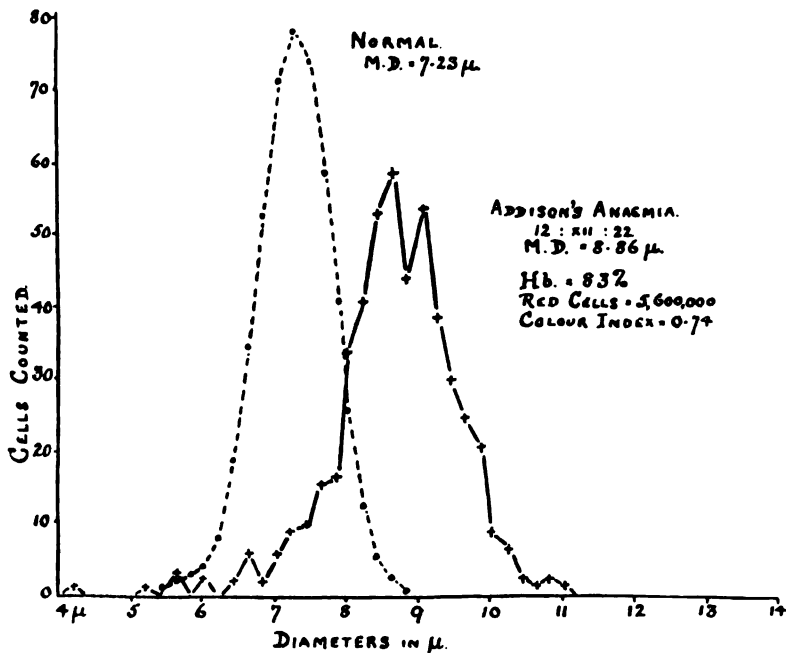


FIG. 5.

A case of Addison's anæmia and subacute combined degeneration of the cord.

not observed in cases of tabes and disseminated sclerosis. It follows, therefore, that cases showing signs of subacute combined degeneration call for careful blood examination, particularly as the hæmoglobin and colour index may be normal.

Case 2.—*A case of subacute combined degeneration of the cord shown to be an early case of Addison's anæmia.*—R. B., male, æt. 49, gave the following history. Nine months previously he experienced a feeling of tingling and numbness in the tips of the fingers; this gradually spread upwards to the elbows. This was followed by a tingling sensation in the skin above the left iliac crest, which spread round the body and down both legs to



the toes. At this period the sensation of a tight strap round the body was felt just below the ribs. He tired more easily and had difficulty in walking. He could not stand with his eyes shut as when washing his face.

On examination the biceps, supinator and triceps jerks were sluggish; abdominal reflexes present; knee and ankle reflexes absent; plantar response flexor; Romberg's sign positive; pupil reflexes normal. There was diminished sensation to cotton wool on both legs, and complete absence of vibration sense below the third lumbar vertebra. There were patches of vitiligo on both forearms, over the clavicles and on the throat. The tongue was clean but fissured. There was some pyorrhœa.

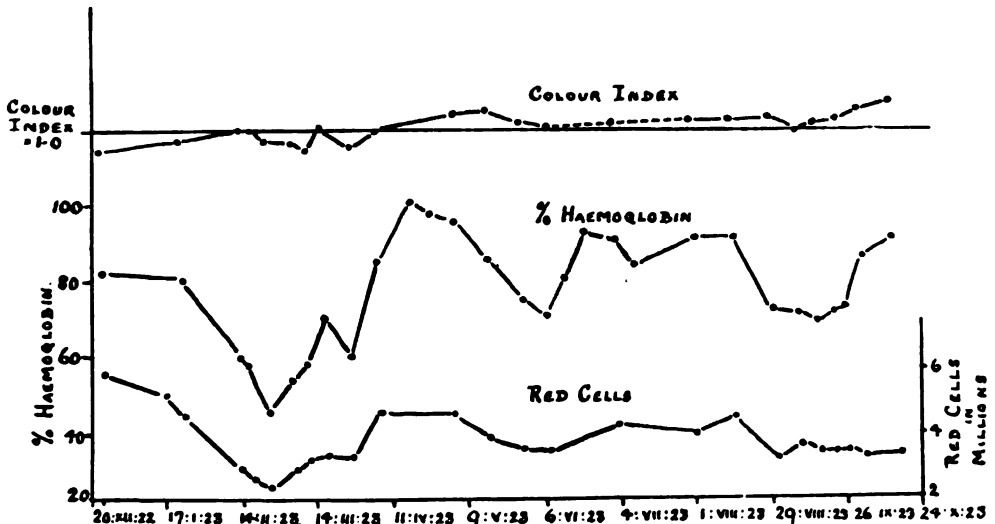


FIG. 6.

Same case as Fig. 5, curves showing variation in hæmoglobin, red cell count, and colour index.

Wassermann's test was negative in blood and cerebro-spinal fluid. A fractional test-meal showed complete achlorhydria. A diagnosis of subacute combined degeneration of the cord was made.

Blood examination showed: hæmoglobin 83 per cent., red cells 5,600,000 per c.mm., colour index 0.74, white cells 4,700 per c.mm.—polymorphs 50 per cent., lymphocytes 47.5 per cent., eosinophils 1.5 per cent., hyalines 1 per cent. One nucleated red cell was seen in a differential count of 500 white cells. There was no poikilocytosis. A cell distribution curve was plotted, as shown in Fig. 5. This was regarded as evidence of Addison's anæmia in spite of the low colour index.

A hæmolytic *Streptococcus longus* was isolated from teeth, stomach and duodenum.

Under observation, the sensory symptoms increased. The course of the blood condition is shown by the accompanying curves (Fig. 6).

At the end of the second month, van den Bergh's test gave a positive indirect reaction, and about the same time a distinct yellow colour was observed in the patient's skin. The blood picture showed many poikilocytes and megaloblasts, polychromasia, and punctate basophilia.

Cases of subacute combined degeneration of the cord may occur in which there is no anæmia and in which there is no megalocytosis, although, as shown in Case 2, megalocytosis may be present before there is anæmia.

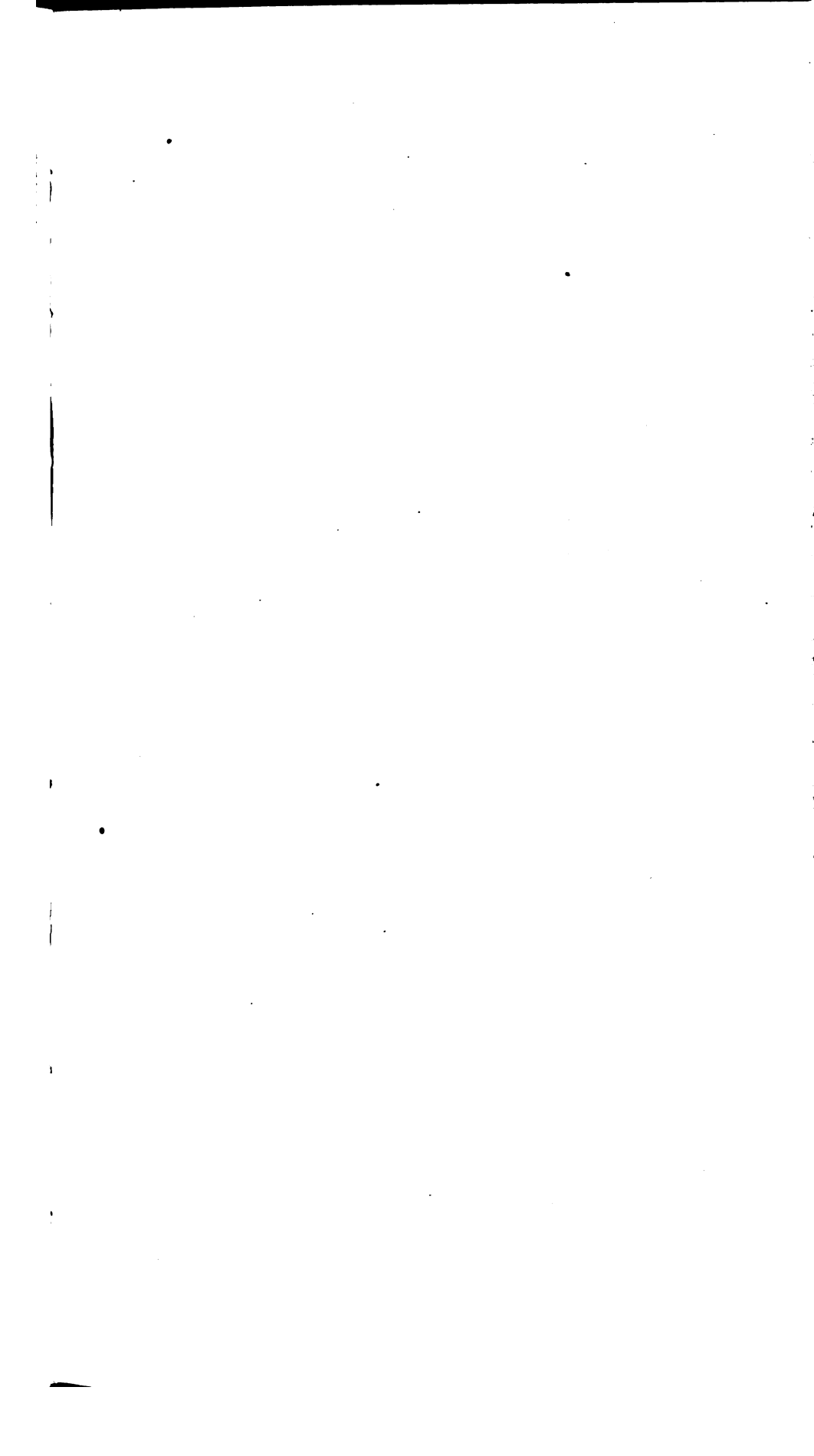
In a typical case of Addison's anæmia, the red cells show the following characters :

1. Anisocytosis.
2. Poikilocytosis.
3. High mean diameter of red cells.
4. Punctate basophilia and polychromasia, especially in the megalocytes.
5. Megaloblasts are present.
6. The cell distribution curve is of irregular conformity.

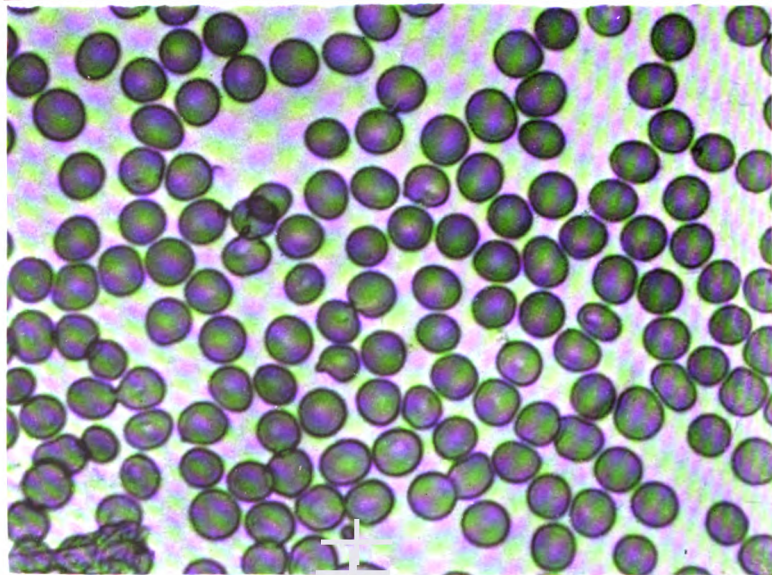
Individual cases may show variations. Case 2 illustrates this. At the time when the first examination of the blood was made, there had been no symptoms of anæmia. Fig. 5 shows that the conformity of the curve was fairly regular, the mean diameter being  $8.85 \mu$ . There was no poikilocytosis nor punctuate basophilia. Under observation the hæmoglobin continually fell. On 15.2.28 (Fig. 6) the hæmoglobin was 58 per cent., and the mean diameter was  $9.90 \mu$ . The picture then showed the typical features enumerated above. The cell distribution curve shows a large number of cells above  $10 \mu$  in diameter (Fig. 7).

During the following week the hæmoglobin fell to 46 per cent. Further investigations have lead us to the conclusion that such a type of curve is usually followed by a fall in hæmoglobin. After this, the hæmoglobin gradually rose, and on 7.5.28 was 95 per cent., the mean diameter was  $8.99 \mu$ , and the curve again became more regular in conformity (Fig. 7). Van den Bergh's test showed a negative indirect reaction on 7.5.28, contrasting with the positive reaction obtained on 16.2.28 and again on 7.6.28. This suggests a temporary remission of hæmolytic at the time of the second curve.

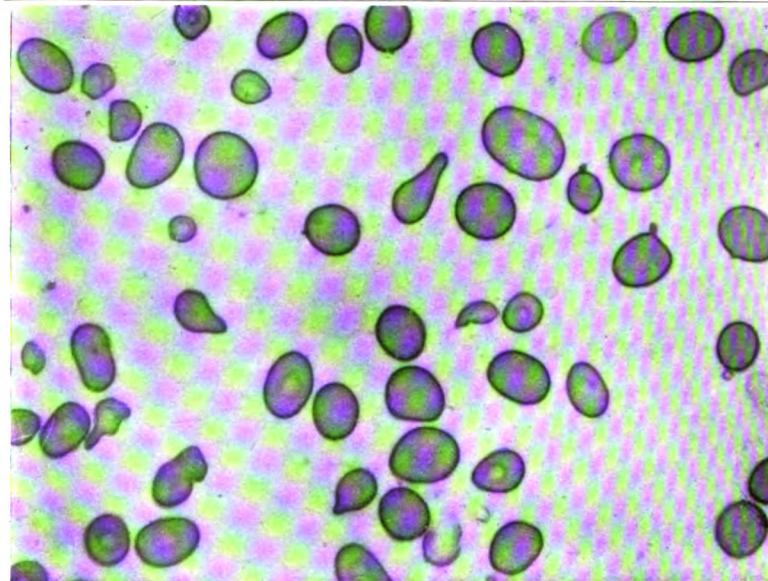
That a high mean diameter of red cells is followed by a fall in hæmoglobin is further illustrated by the following case. It is seen from the accompanying table that the hæmoglobin remained steady at 70 per cent. from 29.1.28 to 14.2.28. On the latter date, the mean diameter had risen to  $10.02 \mu$ . During



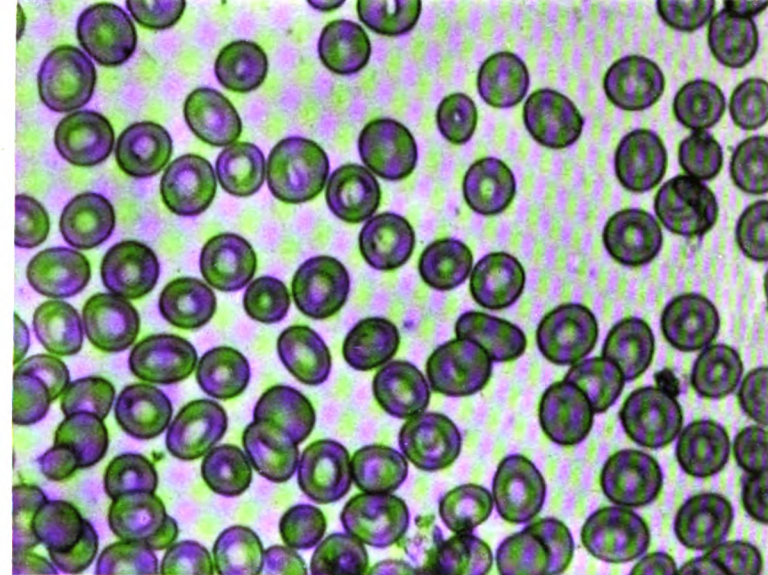
# PLATE I



(a) BLOOD FILM FROM HEALTHY PERSON. MEAN DIAMETER  $7.4\ \mu$



(b) BLOOD FILM FROM CASE OF ADDISON'S ANÆMIA DURING PHASE OF ACUTE HÆMOLYSIS. M.D.  $8.27\ \mu$



(c) BLOOD FILM FROM CASE OF ADDISON'S ANÆMIA DURING REMISSION OF HÆMOLYSIS. M.D.  $8.86\ \mu$

The magnification is the same in the three photographs.

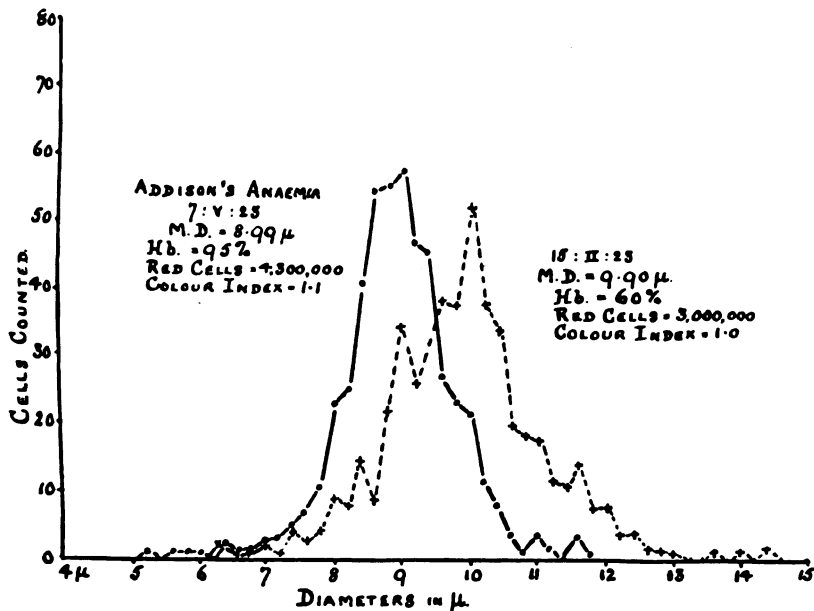


FIG. 7.

Case 2, showing acute phase and temporary recovery.  
(Compare Plate I.)

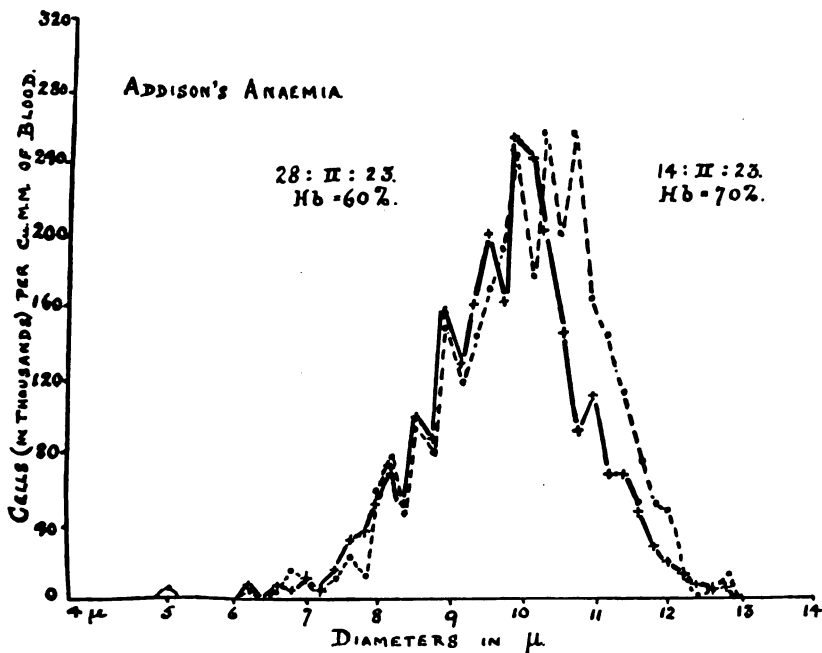


FIG. 8.

A case of Addison's anaemia, showing destruction of large cells during active phase. Curve represents absolute number of cells per c.mm. of blood.

the following week the hæmoglobin fell to 62 per cent., and to 60 per cent. on 28.2.23. The cell distribution curves representing the absolute number of cells per c.mm. for 14.2.23 and 28.2.23 are superimposed in Fig. 8.

<i>Date.</i>	<i>Hæmoglobin.</i>
29.1.23.	70 per cent.
7.2.23.	70 „ „
14.2.23.	70 „ „
21.2.23.	62 „ „
28.2.23.	60 „ „

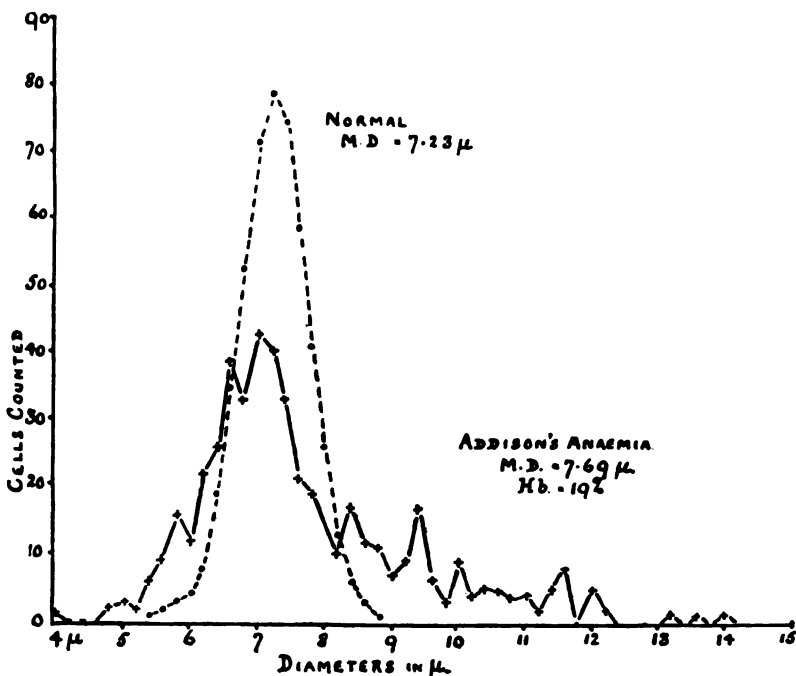


FIG. 9.

A case of Addison's anæmia with low hæmoglobin; picture complicated by transfusions.

These results suggest that the large cells are the most liable to be destroyed. A fall of mean diameter may therefore accompany active cell destruction.

The following curve (Fig. 9) taken from a case of Addison's anæmia, in which extensive cell destruction was taking place, has been selected as showing to the most marked degree the effect of transfusions on the mean diameter, a point which must be taken into consideration where a diagnosis has not been made previous to transfusion. In spite of transfusions,

the hæmoglobin was only 19 per cent. The large majority of cells were within normal limits; these are presumably cells of the donors.

In Addison's anæmia, in the intervals between the active phases, the anisocytosis decreases, and the curve tends to assume a more regular outline. Although in three of the cases examined the hæmoglobin actually reached 100 per cent. (in one of these 110 per cent. was attained), neither in these, nor in several others where a high value of hæmoglobin was

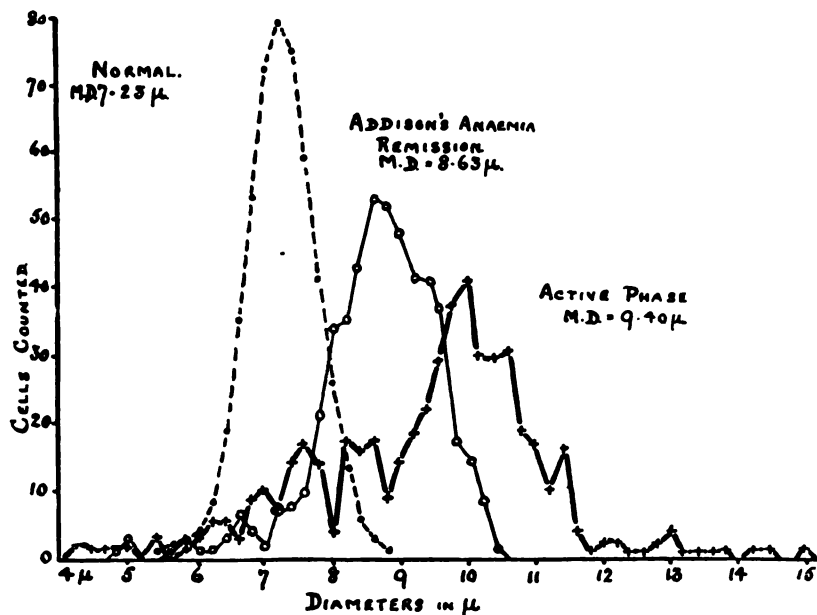


FIG. 10.

Addison's anæmia; active phase and remission (see also Fig. 7).

reached, did the curve become normal or the mean diameter fall to within normal limits—*i. e.* the condition remained megalocytic (Fig. 10).

After splenectomy, although in two cases followed by a temporary rise in hæmoglobin, the blood still remained megalocytic (Figs. 11 and 12).

#### (B) MEGALOCYTIC ANÆMIA IN PREGNANCY

According to Naegeli,<sup>5</sup> the blood picture in pregnancy may show changes similar to those found in Addison's anæmia. We have so far not observed such changes with the exception of the following case.

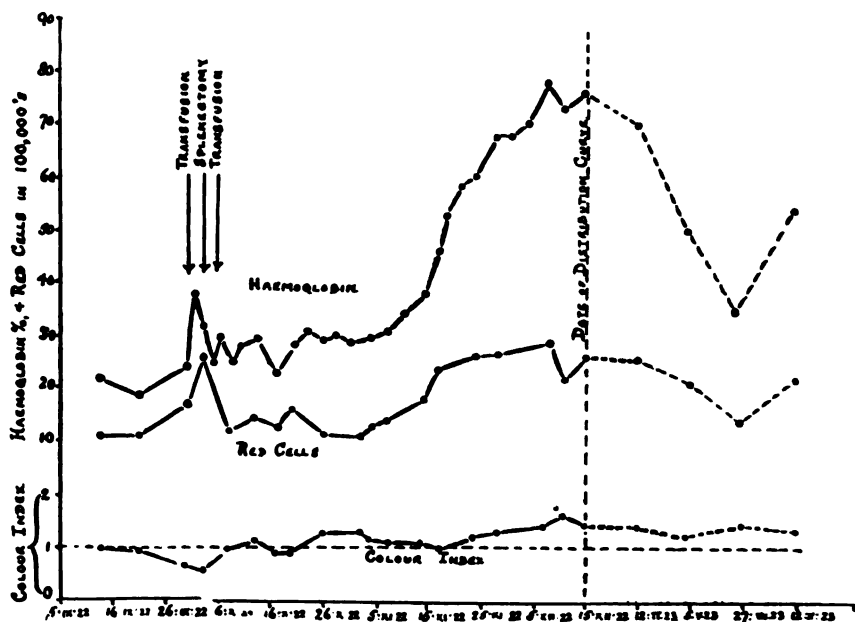


FIG. 11.

Curves showing variation in hæmoglobin, red cell count, and colour index.

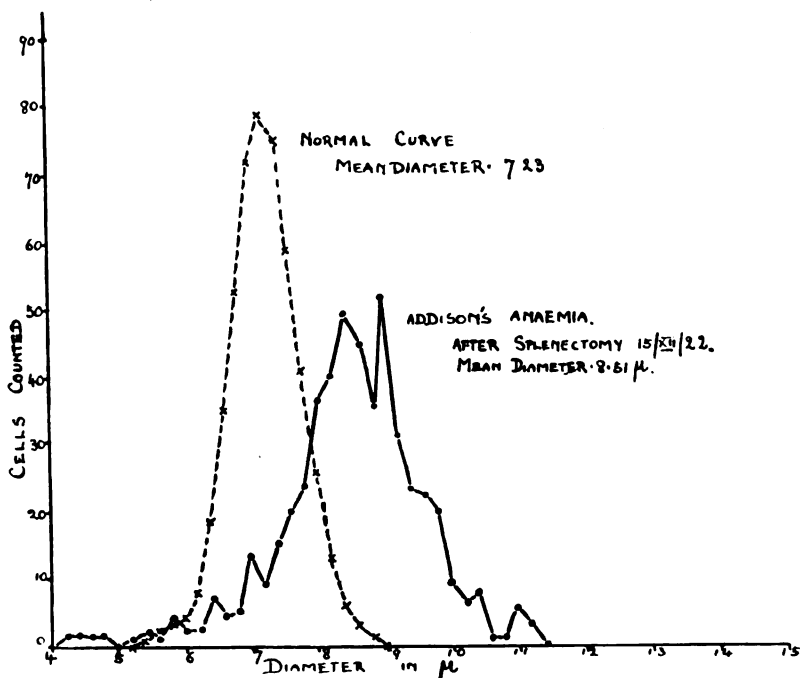


FIG. 12.

Addison's anaemia; after splenectomy (same case as Fig. 11).



Case 8.—*A case of megalocytic anæmia occurring during pregnancy.*—V. P., female, æt. 23, was admitted on 8.11.28 for anæmia and general œdema. When aged three, she had been eighteen weeks in hospital, suffering from scarlet fever and “complications.” From this time onwards she gave an indefinite history of anæmia of a recurrent and progressive character. For some weeks she had been much troubled by ulcers on the tongue and gums, and for three or four weeks the bowels had been very loose. Menstruation commenced when she was aged seventeen, and had always been very irregular. At the time

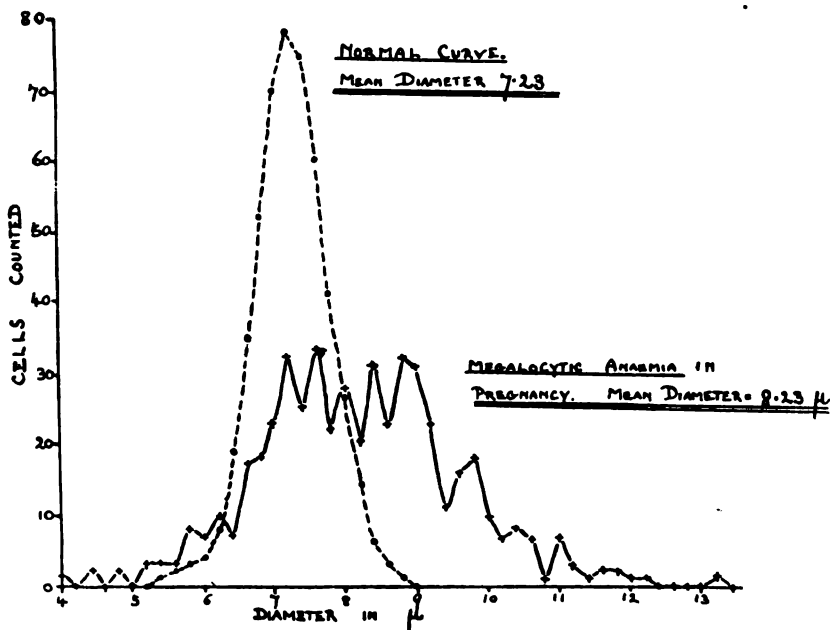


FIG. 13.

Megalocytic anæmia occurring during pregnancy.

of her marriage in March 1928 she was feeling particularly well. Her last period commenced on 10.4.28. For six weeks before admission, patient had been confined to bed with œdema of the legs, hands and face. On examination on four occasions the urine contained no albumin. She had not suffered from headaches. On admission she looked extremely pale. There was a very marked general œdema. Patient was obviously dyspnoic. The heart was not enlarged, but pre-systolic and systolic murmurs could be heard at the apex. The urine contained a trace of albumin. The fetal heart was heard on 4.11.28. While under observation, the extent of the œdema was found to vary, and when this was least marked, patient was seen to have a distinct lemon-yellow complexion. Blood examination showed blood urea 0.87 gms. per 1,000 c.c., hæmoglobin 22 per cent., red cells 1,100,000 per c.mm., colour

index 1.0, white cells 17,000 per c.mm.—polymorphs 76 per cent., lymphocytes 8 per cent., eosinophils 1.5 per cent., hyalines 5 per cent., basophils 0.5 per cent., myelocytes, etc., 9 per cent. Nucleated red cells, chiefly megaloblasts, were present to the extent of 680 per c.mm. There was considerable anisocytosis, poikilocytosis, polychromasia, and punctate basophilia. The cell distribution curve is shown in Fig. 13. Van den Bergh's test gave a negative direct and a well-marked positive indirect reaction. On 11.11.23 patient was spontaneously delivered of a macerated fœtus weighing 2 lbs. There was very little hæmorrhage. On the evening of 15.11.23 she became extremely dyspnœic and comatose. She was transfused with a pint of citrated blood. This temporarily relieved the dyspnœa, but she died the following morning. At autopsy, the marrow showed marked hyperplasia of the red-cell elements; this was almost entirely megalocytic. The heart showed fatty degeneration. The liver gave a well-marked Prussian-blue reaction, confirmed by histological findings. Other organs appeared normal.

From the above history it appears possible that anæmia of an Addisonian type had been present for some time, but there can be little doubt that the gravity of the condition was much increased by the pregnancy.

This case is also of interest, as showing that leucocytosis may occur in megalocytic anæmias. The leucocytosis was polymorphonuclear, and can probably be regarded as the physiological leucocytosis of pregnancy. We have observed a polymorphonuclear leucocytosis in three other cases of Addison's anæmia, as a result of sepsis. In one of these cases, which proved fatal, the leucocytosis was maintained till the end.

### (C) SPRUE

The differentiation of this disease from Addison's anæmia may be very difficult, the clinical features in many cases being almost identical.

Sprue occurs especially in the tropics, but many cases have been reported from the United States, and Low <sup>7</sup> has drawn attention to cases occurring in England.

In the diagnosis of this condition, special stress has been laid upon buccal ulceration, the character of the stools, wasting and anæmia. Buccal ulceration is undoubtedly found both in sprue and in Addison's anæmia; and diarrhœa is commonly found in the latter as well as in the former condition. It is usually stated that patients suffering from Addison's anæmia are well covered; there are marked exceptions to this, however. One patient, with hæmoglobin of 42 per cent. weighed 10 stone, having lost 3 stone 10 lbs. during two and a half years. With

an improvement in hæmoglobin to 110 per cent. a year later, his weight rose to 14 stone 7 lbs. Another patient, with hæmoglobin of 28 per cent., weighed 6 stone 10 lbs. With a rise of hæmoglobin to 60 per cent., the weight gradually increased to 7 stone 7 lbs. A previous continuous fall in hæmoglobin extending over three months was associated with a continuous loss of weight during the same period.

The ætiology of both conditions is obscure. In Addison's anæmia, Hurst <sup>4</sup> has drawn attention to the constant incidence

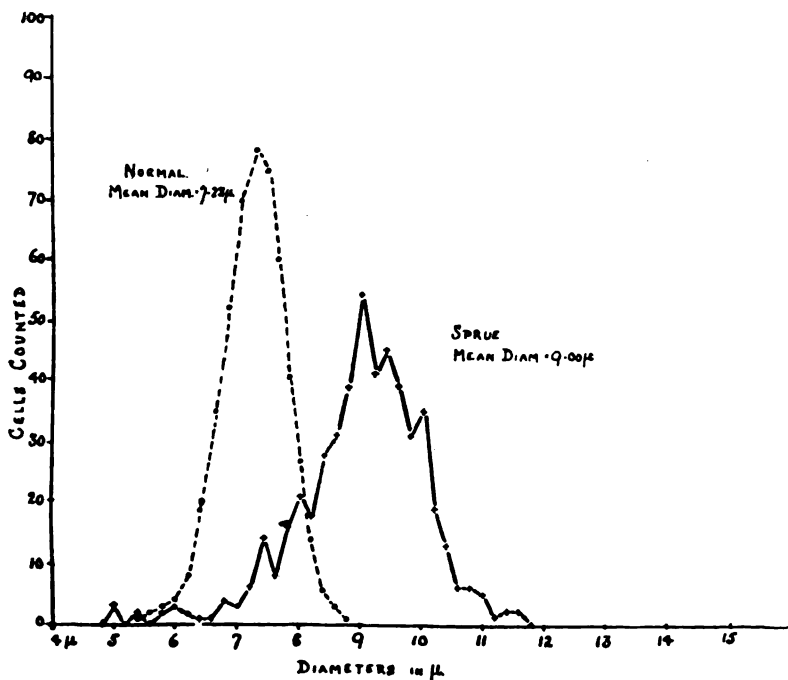


FIG. 14.

A case of sprue.

of achlorhydria. Of the thirty cases included in this series, all showed complete achlorhydria. Of the cases of sprue, five showed complete achlorhydria, and in another case where the stomach tube was not tolerated, an indirect estimation by means of alveolar air by Dr. E. C. Dodds showed achlorhydria. In two cases free hydrochloric acid was present. In the remaining four cases no estimation of gastric acidity was made. According to Scott,<sup>6</sup> however, there may be hyperchlorhydria in sprue.

In both Addison's anæmia and sprue marked remissions occur. Many cases have been regarded as cured, relapses

occurring even after an interval of years. Dr. G. C. Low <sup>7</sup> has drawn attention to this point in the case of sprue.

The twelve cases of sprue in this series comprise cases at the London Hospital for Tropical Diseases, and cases under the care of Dr. A. F. Hurst. In every case a typical megalocytic condition of the blood was found (Fig. 14).

With regard to the blood-picture in sprue during the remissions we have not obtained much evidence. None of the twelve cases were examined on more than one occasion, but it

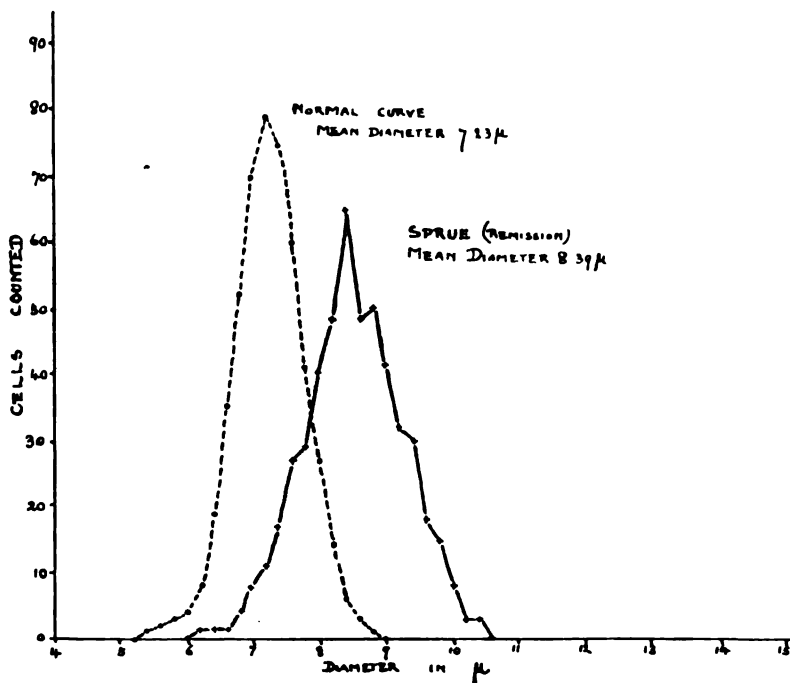


FIG. 15.

A case of sprue with high hæmoglobin.

was noted that in several instances, where there was a high percentage of hæmoglobin, distribution curves were of the comparatively symmetrical configuration described above as occurring during remissions in Addison's anæmia, whereas in cases where there was a low percentage of hæmoglobin the curve was of irregular conformity, as shown in Fig. 14.

Van den Bergh's test was only done in three cases; all gave a negative direct but positive indirect reaction, as in Addison's anæmia.

The difficulty in diagnosis between Addison's anæmia and sprue is well illustrated by the following case, diagnosed as Addison's anæmia by Dr. A. F. Hurst, and as sprue by Dr. G. C. Low.

Case 4.—*Addison's anæmia or sprue*.—M. P., female, æt. 65, gave a history of diarrhœa, buccal ulcers, weakness and wasting following an attack of acute gastro-enteritis while staying in New York. She had lived for many years in Barbadoes. She had lost two stone in weight since June 1922. Motions were frothy and of light colour; there was no mucus or blood. Patient had a distinct lemon-yellow complexion. On investigation, fæces were acid to litmus and showed excess of fatty acids and soap crystals. No cysts were present. A fractional test-meal showed complete achlorhydria. Bacteriological examination of duodenal specimens failed to show streptococci, but

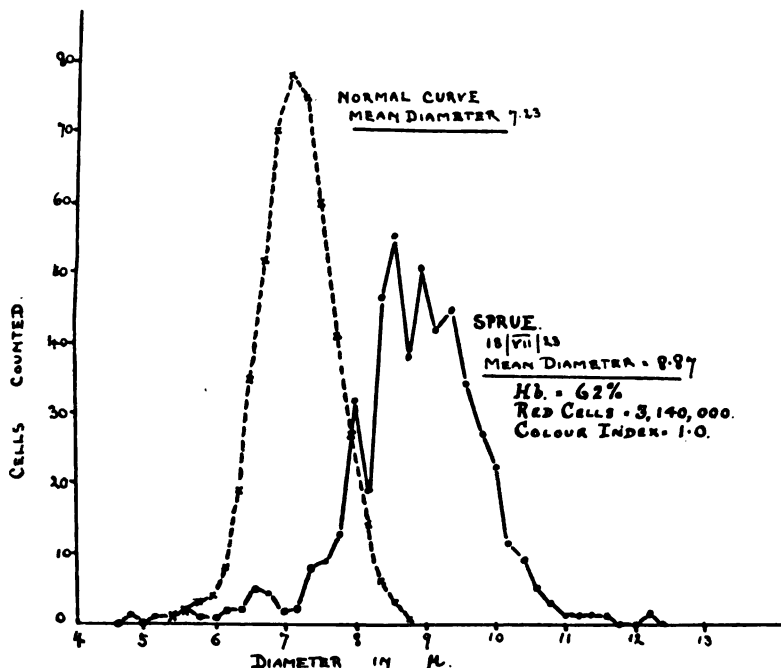


FIG. 16.

Case of Addison's anæmia or sprue.

the patient had been taking large doses of dilute hydrochloric acid, which experience shows leads to the rapid disappearance of streptococci from the duodenum in Addison's anæmia. Van den Bergh's test showed a weak positive indirect reaction. Knee jerks were only obtained on reinforcement. Left ankle jerk was weak and right ankle jerk was absent. Abdominal reflexes were absent. Blood examination showed hæmoglobin 62 per cent., red cells 3,140,000 per c.mm., colour index 1. There was marked poikilocytosis. Many cells showed polychromasia. There were some megaloblasts. White cells 8,800 per c.mm.—polymorphs 59 per cent., lymphocytes 28 per cent., hyalines 10 per cent., eosinophils 2 per cent., basophils 1 per cent. The red-cell distribution curve is shown in Fig. 16.

## (D) LEUKÆMIA

Cases have been described in which the blood, in addition to showing a leukæmia, has shown a red-cell picture which has been stated to resemble that of Addison's anæmia. We have not observed such a case. In one instance we examined films from a case which was supposed to show such changes; the red cells, however, were non-megalocytic.

## ALEUKÆMIC LEUKÆMIA

The blood was examined in three cases of so-called aleukæmic leukæmia. In two of these the cells were non-megalocytic; in the third case (Case 5) the blood-picture was identical with that found in Addison's anæmia.

Case 5.—*A case of aleukæmic leukæmia.*—F. H., male, æt. 42, was admitted for swollen glands in the neck, axillæ and groins. Patient gave a history of dysentery in 1915, while serving in Gallipoli. He was in Hospital six weeks for this condition. He contracted syphilis in 1920: he was treated regularly for two years. After this he gave a negative Wassermann reaction on five occasions. About a week before Christmas 1923, he had a feverish attack lasting two days. There were no other symptoms. He stayed in bed two days and then felt quite fit again. About a week later he noticed lumps below and behind the ear. The following week, lumps were noticed in both axillæ and groins. The lumps remained much the same size and were only slightly tender to pressure. He felt weary and listless. There was some nausea after meals, and occasional vomiting. Bowels were regular but rather loose. On admission he appeared well-nourished. Glands were found along the anterior and posterior borders of both sterno-mastoid muscles, in the right submaxillary region, in both axillæ and groins. The glands were discrete, gave an impression of elastic firmness and were easily movable. The lower pole of the spleen was felt to extend to two fingers' breadth below the costal margin. The liver was not palpable. The tongue was moist and clean. He was edentulous. Blood examination on 12.2.24 showed hæmoglobin 92 per cent., red cells 4,670,000 per c.mm., colour index 0.97, white cells 4,700 per c.mm.—polymorphs 24 per cent., lymphocytes 57 per cent., hyalines 10 per cent., myelocytes, etc., 9 per cent., nucleated red cells 141 per c.mm., many of which were megaloblasts. Many cells showed polychromasia and punctate basophilia. There was some poikilocytosis. The red-cell distribution curve is shown in Fig. 17.

Van den Bergh's test gave a well-marked positive indirect reaction. A test-meal showed hypochlorhydria. The chloride curve, however, shows that the hypochlorhydria was due to excessive neutralisation (Fig. 18).

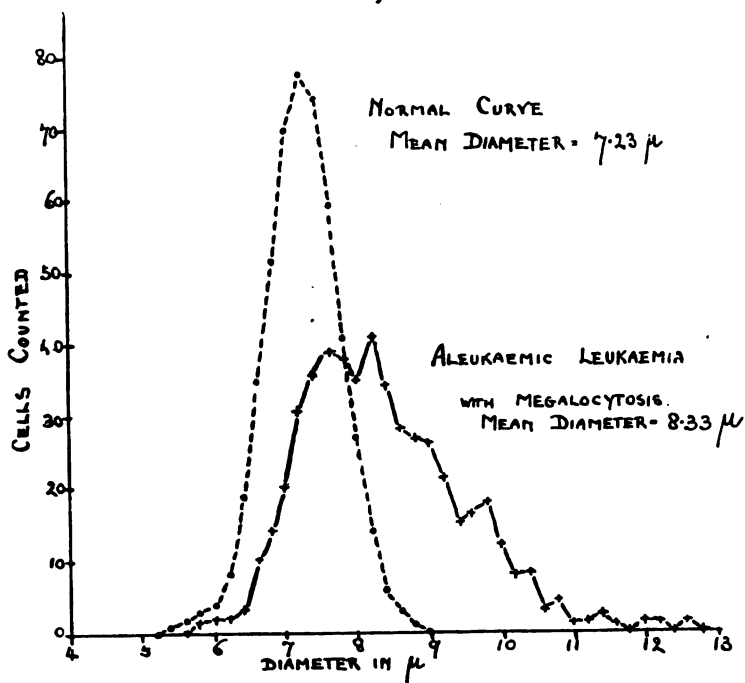


FIG. 17.  
A case of aleukæmic leukaemia.

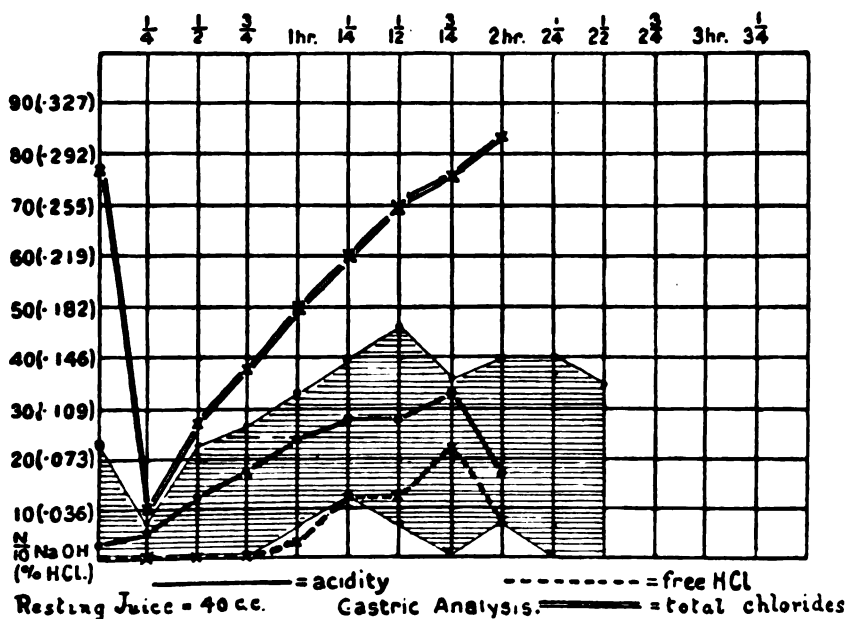


FIG. 18.  
Result of fractional test-meal in Case 5. The shaded area represents the limits of free HCl (dimethyl indicator) of 80 per cent. of normal people.

On 14.2.24 the spleen was found to extend to three fingers' breadth below the costal margin. The abdomen was distended, with some free fluid, and there was œdema of the scrotum and the lumbar pad.

After two days' pyrexia, he died on 18.2.24, of what was apparently an intercurrent infection of an influenzal type, which was then prevalent in the ward. At autopsy, enlarged glands were found throughout the body; the spleen was uniformly enlarged. Nodules were found in the intestinal mucous membrane. The marrow showed hyperplasia of the red-cell elements. Sections of glands and nodules were examined by Prof. Adrian Stokes, who considered the case to be one of aleukæmic leukæmia.

If the pseudo-leukæmic condition commenced with the febrile attack at Christmas 1923, it seems doubtful whether such a degree of megalocytosis would develop in so short a time. Possibly some stress ought to be laid on the history of dysentery in 1915.

#### (E) INFANTILISM

In a discussion on renal dwarfism at a meeting of the Royal Society of Medicine in 1920, Tidy<sup>8</sup> described a case of a boy who had been diagnosed as a renal dwarf. He showed definite bone changes when aged four. When aged thirteen he was sent home from a public school, as he was stated to be suffering from "pernicious anæmia." His hæmoglobin was then 45 per cent., red cells were 2,000,000 per c.mm., colour index 1.1. Normoblasts, megaloblasts and myeloblasts were found. The spleen was enlarged. A year later he was stated to be much better. The spleen was smaller, hæmoglobin was 65 per cent., red cells were 3,000,000 per c.mm., colour index 1.1. Only occasional normoblasts and megaloblasts were seen. There had been no albuminuria. The following case appears to be of a similar nature :

Case 6.—*A case of infantilism associated with megalocytosis.*—K. S., female, æt. 16, was admitted for genu valgum. The condition was first noticed about three years previously. She was unable to run and her knees hurt on walking. She was very small for her age, and from an x-ray examination of her epiphyses, a diagnosis of renal dwarfism was made. An examination of the urine showed a few blood-casts, a minute trace of albumin, and excess of urobilin. On a number of other occasions no albumin was found. The fæces contained a slight excess of soap crystals. An examination of the blood showed blood urea 0.13 gms. per 1,000 c.c.—a low value corresponding to low metabolism—hæmoglobin 54 per cent., red



cells 3,420,000 per c.mm., colour index 0·8, white cells 4,800 per c.mm.—polymorphs 50 per cent., lymphocytes 42 per cent., hyalines 6 per cent. eosinophils 2 per cent., some poikilocytosis and polychromasia and nucleated red cells. Van den Bergh's test gave a positive indirect reaction. The red-cell distribution curve is shown in Fig. 19.

Two other cases of infantilism were examined: neither showed any megalocytosis.

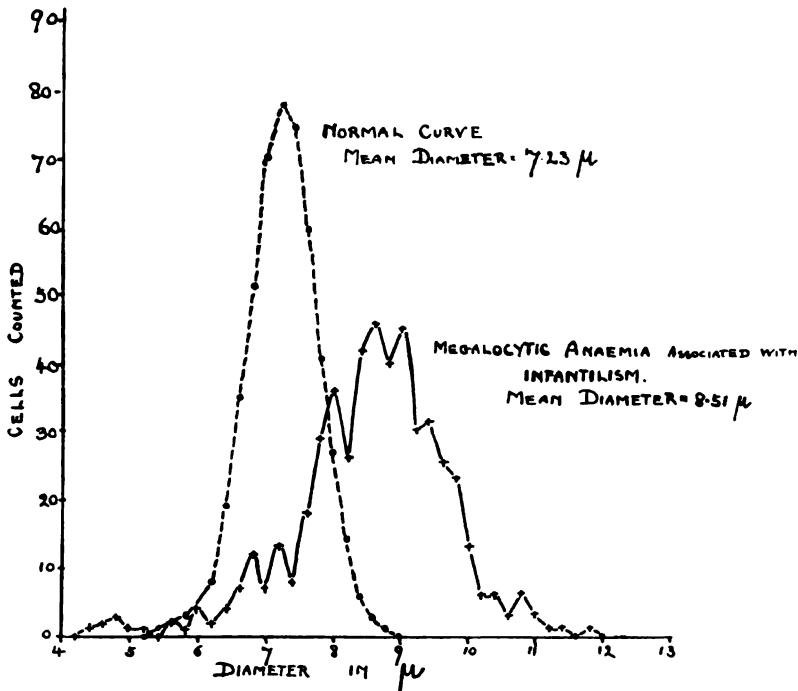


FIG. 19.

A case of infantilism, associated with megalocytosis.

#### *Relation of Megalocytosis to Hæmolysis*

The above investigations point to two outstanding facts:

(1) That the blood may be megalocytic in the absence of any evidence of hæmolysis. As stated above, a high value of hæmoglobin has been maintained over considerable periods, during which van den Bergh's test has given a negative direct and indirect reaction. At such times the conformity of the cell distribution curve was symmetrical, a finding which would not be expected if hæmolysis were taking place.

(2) That if the blood in such cases be examined at intervals, asymmetrical curves are obtained, associated with hæmolysis

and a positive indirect van den Bergh's reaction. This may be followed by a rise in hæmoglobin and a return to a symmetrical megalocytic curve.

It would appear, therefore, that megalocytosis and hæmolysis are due to separate factors. Much has been written suggesting that megalocytosis is due to a response on the part of the marrow to the anæmic condition. Hunter<sup>9</sup> states that the anæmia is hæmolytic in nature, toxic in origin, and the bone marrow changes are secondary and compensatory to the destruction. If this be the case, it would be expected that the megalocytosis would bear some relation to the degree of anæmia. In several of the cases in this series the degree of anæmia had certainly never been sufficiently marked to attract attention, although megalocytosis was well marked when the blood was first examined, and, as stated above, the highest degree of megalocytosis was found to precede an acute hæmolysis.

We desire to express our sincere thanks to all those who have given us such free access to their cases. Our especial thanks are due to Dr. A. F. Hurst and Dr. G. C. Low, to whom we are indebted for much valuable material.

#### ADDENDUM

##### (F) *Bothriocephalus Anæmia*

Since this paper was written we have examined films from a case of bothriocephalus anæmia, kindly sent to us by Professor T. W. Tallquist of Helsingfors, Finland. They show typical megalocytosis.

TABLE I.

## MEGALOCYTIC ANÆMIAS.

Distribution of Red Cells in Representative Cases of Addison's Anæmia and Sprue.

Diam. in $\mu$ .	Addison's Anæmia Cases.																				Sprue.		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1	2	3
4.0				1	1									1	1	0							
.2	1			0	0								0	1	2	2		1					
.4	—			2	5	1					1	1	1	1	1	1		1					
.6	—			0	2	1					1	0	1	0	1	2	1	1					
.8	—			0	2	0					1	1	1	2	2	1	1	1					
5.0	—			0	6	1		1	0	2	0	1	3	3	1	1	2	0		1	2	1	3
.2	1			3	0	5		0	0	0	0	3	2	1	3	0		1	0				0
.4	0			3	4	0		1	1	0	3	3	6	3	1	3		2			1	1	1
.6	3			3	6	0		2	1	2	5	0	1	9	7	2	0	1	1		2	2	0
.8	0		1	8	9	0		3	4	3	4	9	16	8	3	2	1	0			2	1	2
6.0	2	1	3	7	10	5	2	3	2	1	4	7	12	3	4	3	2	2	1	5	1		3
.2	0	0	0	10	8	2	1	3	2	1	6	5	22	9	5	5	5	2	0	7	2	1	2
.4	2	2	1	7	21	1	2	4	3	2	8	13	26	10	10	5	4	9	2	4	2	1	1
.6	6	0	2	17	11	2	4	5	6	3	10	8	39	10	5	3	2	4	2	2	5	1	1
.8	2	6	7	18	18	5	2	3	5	4	18	7	33	12	7	9	3	5	10	2	4	4	4
7.0	6	4	11	23	21	10	4	9	11	4	28	6	43	17	12	10	9	13	18	2	2	8	3
.2	9	3	7	32	13	10	7	4	7	8	42	7	40	15	12	7	19	11	32	2	2	11	6
.4	10	8	12	25	20	17	12	7	10	7	51	20	33	19	13	14	21	15	35	5	8	17	14
.6	16	9	16	33	20	20	12	14	12	11	58	20	21	11	12	17	21	20	46	5	9	27	8
.8	17	15	12	22	18	18	14	10	8	15	50	23	19	17	14	14	23	23	63	9	13	29	16
8.0	34	13	16	28	22	35	27	22	14	17	49	38	25	25	15	4	32	36	50	21	32	40	21
.2	41	31	25	20	23	36	31	17	13	14	48	34	10	40	27	17	21	40	53	29	19	48	18
.4	53	35	12	31	28	56	42	26	31	17	39	38	17	45	23	16	32	49	58	17	47	65	28
.6	59	35	14	23	20	48	34	36	25	27	35	45	12	26	19	17	27	44	42	19	56	48	31
.8	44	42	21	32	19	48	37	29	23	34	15	36	11	32	21	9	39	35	38	19	38	50	39
9.0	54	47	27	31	27	45	59	32	45	42	9	41	7	32	27	14	36	52	30	26	51	41	54
.2	39	35	21	23	19	32	49	43	35	40	8	28	9	26	25	18	35	31	11	31	42	32	41
.4	30	56	36	11	22	35	41	41	47	41	8	29	17	26	37	22	51	23	10	26	45	30	45
.6	25	33	29	16	23	25	33	38	31	40	4	22	6	18	35	29	36	22	5	31	34	18	39
.8	21	30	40	18	15	12	20	39	31	34	2	19	3	17	24	37	29	20	3	39	27	15	31
10.0	9	28	40	10	22	18	19	28	24	37	1	14	9	14	28	41	17	9		51	22	8	35
.2	7	15	39	7	20	2	11	21	27	21		6	4	9	18	30	12	6		37	11	3	19
.4	3	16	34	8	11	3	16	21	19	16		7	5	3	22	30	8	8		29	9	3	13
.6	2	11	16	7	5	3	7	8	23	19		1	5	2	13	31	7	1		22	5		6
.8	3	6	12	1	4	1	4	12	13	10		3	4	3	14	19	3	1		17	3		5
11.0	2	9	17	7	11	1	2	6	9	9			4	1	13	17	2	6		10	1		
.2		5	12	3	3	1	0	1	3	6	3		2	1	5	10	0	3		2	1		1
.4		3	3	1	1	0	0	0	3	3	7				11	16	2				1		
.6		0	3	2	2	0	2	4	5	0			8		4	4	0			10	1		2
.8		0	5	2	1	0	0	1	1				0		0	1	0						
12.0		1	2	1	3	0	0	0	2				5		4	2	1			5	2		0
.2			1	1	0	0	1	0			1		2		3	2				1	1		
.4			0	0	0	1					2					1							
.6			0	0	0								0			0							
.8			0	0	0								0			0							
13.0 and over			1	2	1								3		1	11							

TABLE II.

HÆMOGLOBIN, RED-CELL COUNT, COLOUR INDEX AND MEAN DIAMETER IN REPRESENTATIVE CASES OF ADDISON'S ANÆMIA.

	Case of Addison's Anæmia shown in Table I.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
% Hæmoglobin	83	75	26	22	36	56	45	28	45	34	50	45	19	41	25	20	70	70	—	41
Red cell count (in millions).	5.6	2.96	—	1.14	1.8	2.85	2.2	1.1	1.52	1.54	2.04	2.04	.88	1.51	0.9	.80	3.52	2.4	—	1.66
Colour index.	.74	1.27	—	1.0	1.0	1.0	1.01	1.27	1.48	1.1	1.2	1.1	1.08	1.36	1.4	1.25	1.0	1.4	—	1.24
Mean diameter.	8.86	9.15	9.34	8.23	8.27	8.55	8.90	9.09	9.17	9.17	7.81	8.34	7.69	7.95	8.78	9.40	8.74	8.51	8.05	9.35

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## VARIATIONS IN THE SIZE OF THE RED CELLS IN SOME EXPERIMENTAL ANÆMIAS IN RABBITS

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(From the Pathological Department, Guy's Hospital.)

DURING the summer of 1928 the effects on rabbits of daily injections of a hæmolysin obtained from a hæmolytic streptococcus were observed. The changes in the blood picture were followed with special attention to the variations in the size of the red cells. Without entering here into detailed accounts of the changes so produced, it is sufficient to state that a severe degree of anæmia resulted from the treatment. In studying the blood films it at once became evident that a change in the size of the red blood corpuscles was a striking feature. M'Leod and McNee (1912),<sup>1</sup> in performing similar experiments, had noted, among other changes, a great variability in the size of the red cells. It is to this production of large red cells that we wish to draw attention.

In this series of three rabbits the progress of the anæmia was characterised by the number of large red cells in the picture, with the resulting definite increase in the average diameter of the cells, and a polychromasia of the large cells, changes which were first described by Price-Jones in his work on experimental anæmias produced in rabbits by means of hæmorrhage and phenylhydrazine (1910).<sup>2, 3, 4</sup> When the distribution of the red cells was plotted out in graph form a curve identical with that found in Addison's anæmia resulted. That is to say, compared with the normal, the curve had moved to the right, the usual regularity and uniformity were lacking, and an increased variation in size was demonstrable.

As another method of destroying the circulating red cells, a rabbit was given intravenous injections of saponin. A blood-picture resembling that of Addison's anæmia resulted, and graphs demonstrated the same changes in the cell distribution curve as were found in the rabbits injected with the streptococcal hæmolysin.

The changes which occur in the sizes of the red cells after hæmorrhage were next followed. Three rabbits were used; in two the anæmia was produced slowly by bleeding the animals

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a few cubic centimetres daily, and in the third the anæmia was produced suddenly by means of one single large hæmorrhage.

Examination of the cell distribution curves showed that there had been a considerable production of cells larger in size than the normal, and that when the curves of these three animals were compared, they were all found to be similar in type. When the curves obtained from the bled animals are contrasted with

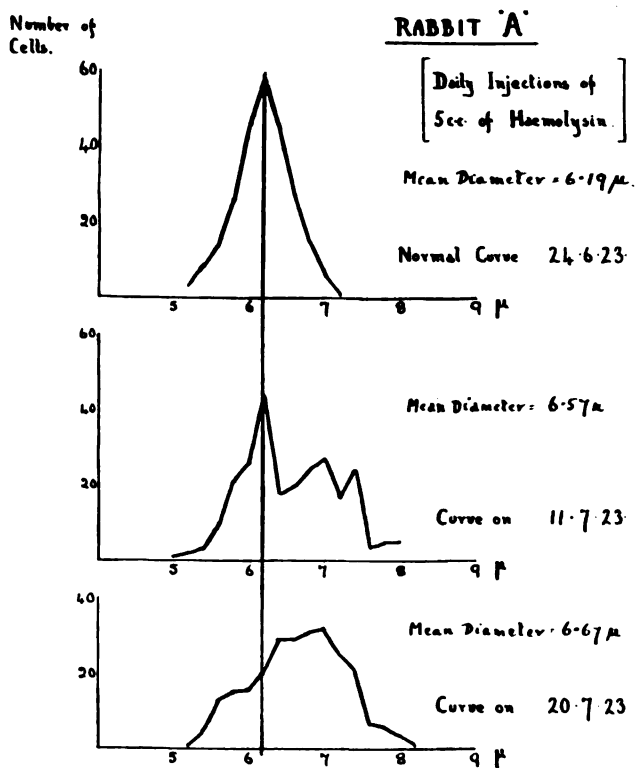


FIG. 1.

Curves showing the effect of Daily Injection of Hæmolysin.

those obtained from the animals injected with hæmolysin and saponin, it will be noticed that almost identical changes have occurred in all of them. In all the curves there is a pronounced movement of the curve towards the right, indicating the appearance in the blood stream of a larger type of red cell than is normally present, and there is no extension of any of the curves towards the left to indicate that there is an increase in the number of cells of small size. In addition it may be pointed out that, in whatever manner the anæmia has been produced, the cells of greatly increased diameter all show polychromasia.

If the cell-distribution curves obtained later on in the hæmoly-sin and slow hæmorrhage experiments be compared, it will be seen that after the initial marked increase in size there is a gradual movement back towards the normal distribution, even though the treatment was still being carried out. This may be due to the power of the blood-forming tissues to accommodate

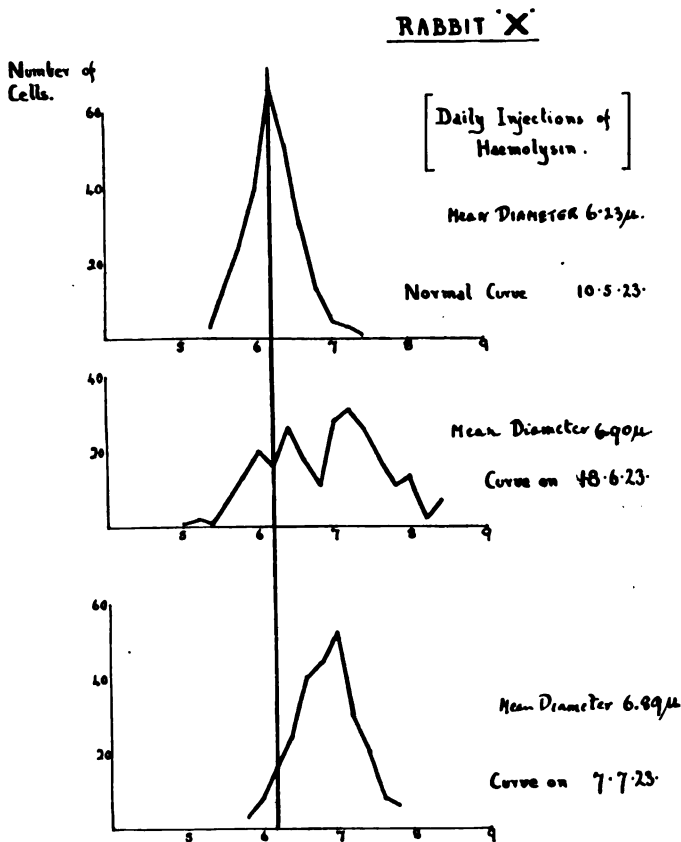


FIG. 2.

Curves showing the effect of Daily Injection of Hæmoly-sin.

themselves to the injury inflicted. Below are given the details of the three series of experiments.

### 1. THE EFFECT OF THE INJECTION OF HÆMOLYSIN

The hæmoly-sin used in this experiment was prepared from a fifteen-hour growth of a streptococcus on broth, to which 1 c.c. of horse serum to every 4 c.c. of broth had been added. The streptococcus selected was one with active hæmolytic properties, and the same strain was used throughout the experiment.

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The cultures were filtered through sterile porcelain filters and immediately injected into the marginal vein of the rabbits. The efficiency of the filters was frequently tested, but on no occasion was a streptococcus grown from the filtrate.

Three animals were used, rabbits A, "X," and Y. Rabbit A was given 5 c.c. daily, whereas X received varying amounts, and Y the same amount as X. The actual amounts given are

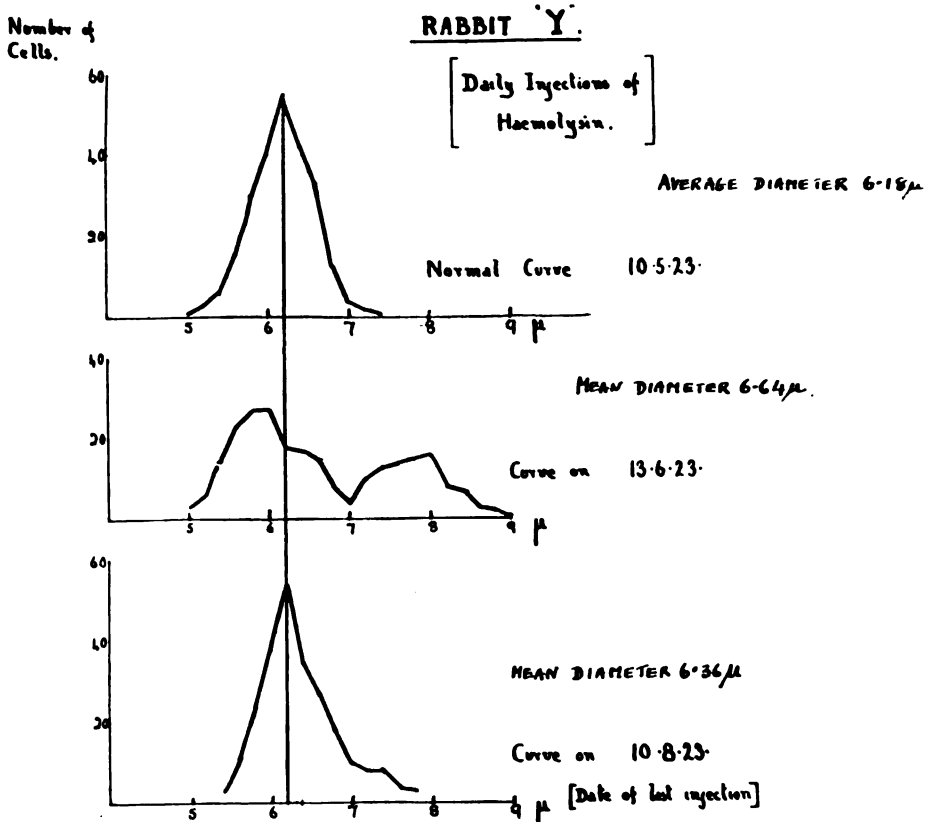


FIG. 3.

Curves showing the effect of Daily Injection of Hæmolytin.

stated in the protocols at the end. Blood counts and films were made about 10 a.m. each day, so as to obtain uniformity and to eliminate the possible factor of diurnal variation in size which Price-Jones has found to occur in man (1920).<sup>5</sup>

Rabbit X was killed after two months of the injections; throughout this period it had appeared perfectly well and active. On post-mortem examination the only demonstrable abnormalities were marked iron reactions in the kidneys, liver



and spleen, and a considerable hyperplasia of the red marrow, which extended the whole length of the shafts of the long bones.

Rabbit A died unaccountably at the end of one month's treatment; it appeared to be quite well a few hours before death

RABBIT 'F'

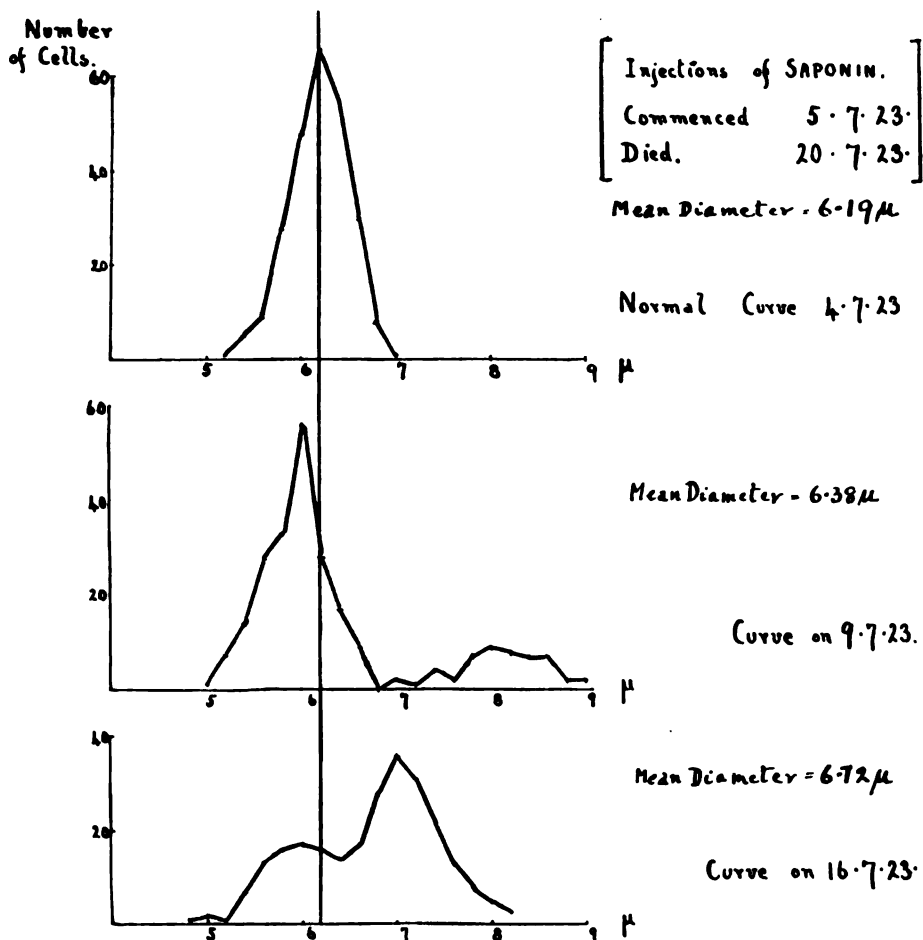


FIG. 4.

Curves showing the effect of the Injection of Saponin.

occurred. Post-mortem nothing was found to account for death. Cultures of the heart blood were sterile. The iron reactions of the tissues were similar to those of rabbit X, though not quite so pronounced. The marrow of the shafts of the long bones was a chocolate-red colour, and could be removed as a cast of the medullary cavity. Rabbit Y survived the experiment.

It is to be noticed that rabbit A received the smaller amount of the toxin and yet succumbed to the treatment, which bears out the statement of M'Leod and McNee that there is a considerable variation in the susceptibility of these animals to the hæmolysin (1912).<sup>1</sup> This too is shown by rabbits X and Y, which, although receiving the same dosage, were affected to a very different extent, as shown by the variation in the degree of anæmia produced, Y being more susceptible than X.

The changes in the curves are shown by the graphs (Figs. 1, 2, 3), which illustrate the general movement to the right and the variability in the size of the cells such as are found in Addison's anæmia (1922).<sup>6</sup>

#### THE EFFECTS OF THE INJECTION OF SAPONIN

Rabbit F. In this animal the destruction of the red cells was brought about by the injection of small quantities of saponin intravenously. This experiment only extended over a short period, as the animal died suddenly on the fifteenth day. The effect of these injections on the cell distribution curves was to produce changes exactly comparable to those obtained in the previous experiment with hæmolysin, namely, an early appearance of cells having a diameter larger than that of any cell found in the normal blood, with a corresponding fall in the normal peak of the curve. Later this peak moved to the right and the very large cells first noticed disappeared (Fig. 4).

This animal did not live long enough to show the swing back to the normal position indicating the accommodation of the bone marrow to the injury.

No cause of death could be found on post-mortem examination. The same iron reactions were obtained as in the hæmolysin experiment, though the marrow was a much darker red, and of a more solid consistency.

#### THE EFFECT OF HÆMORRHAGE

In order to ascertain the effect of hæmorrhage upon the size of the red corpuscles of the rabbit the three following experiments were carried out :

1. A single large hæmorrhage of 60 c.c.
2. A small daily loss of blood.
3. A small daily loss of blood followed by the re-injection into the animal of the hæmoglobin obtained from the amount of blood removed.

Rabbit C. 60 c.c. of blood were removed from the marginal

vein of the ear. Following this daily measurements of the red cells were made, and the distribution curves prepared. Though films were taken during the bleeding, and also as soon as it had

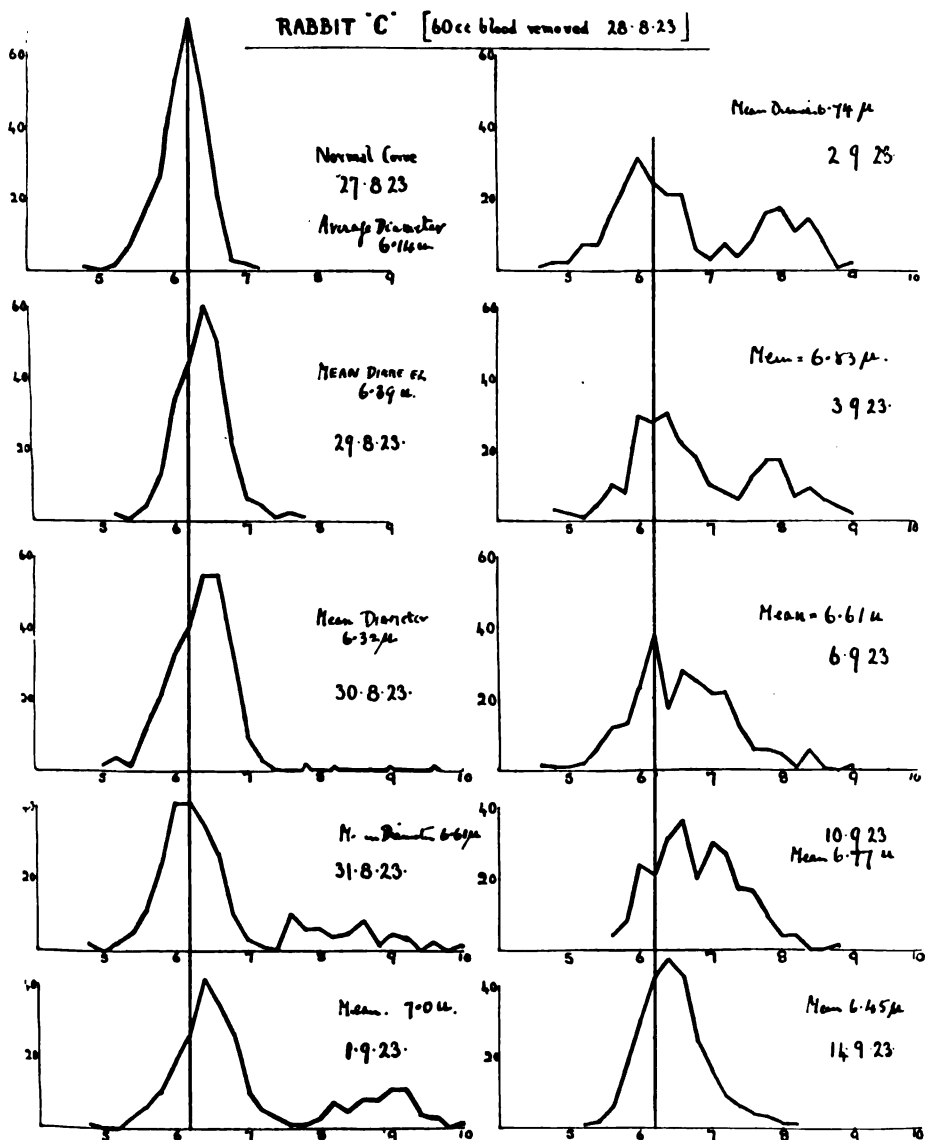


FIG. 5.

Curves showing the effect of One Sudden Hæmorrhage.

ceased, no definite changes in the distribution curves were to be seen until the end of forty-eight hours after the animal had been bled (Fig. 5). It was then seen that there was an increased

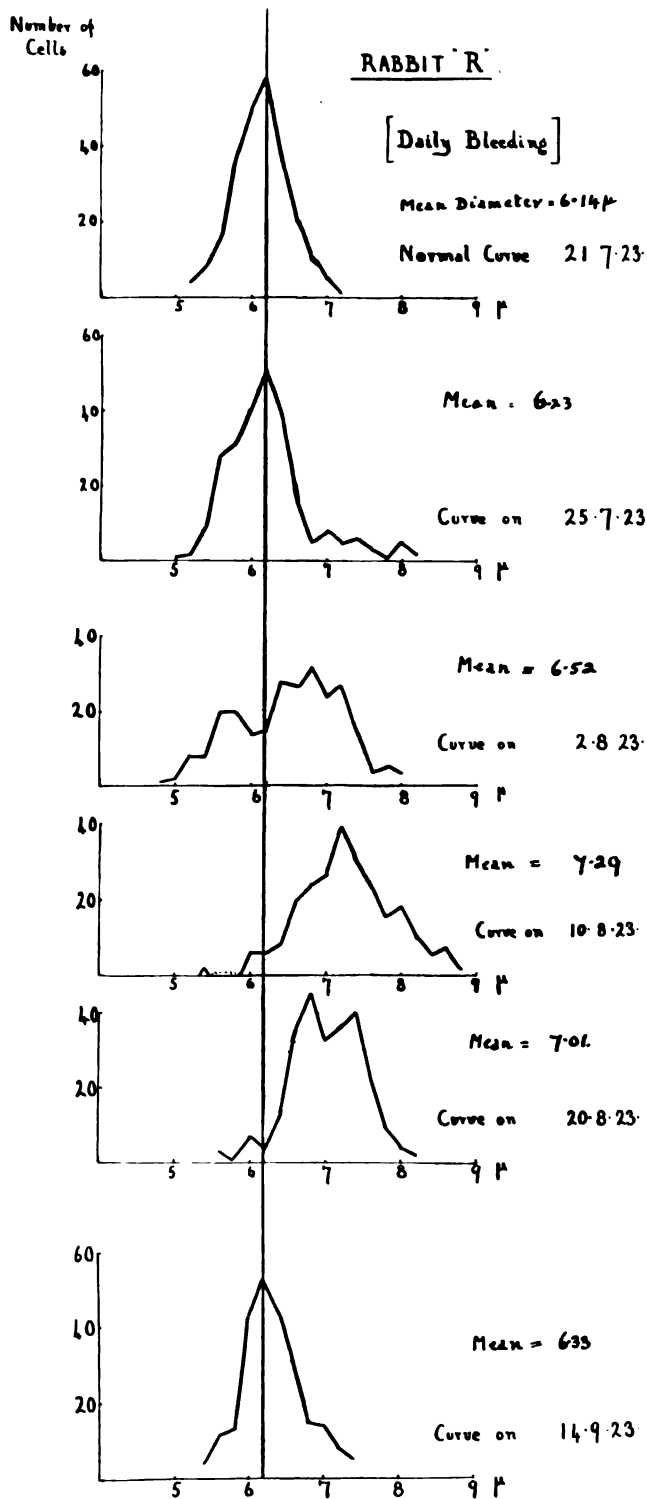


FIG. 6.

Curves showing the effect of Repeated Small Hæmorrhages.

number of cells having a diameter of  $7\ \mu$  and over. Some of these diameters were increased up to  $9.6\ \mu$ . These very large cells further increased in number and size on the third and fourth days, the largest cells appearing on the latter day, when one red cell with the average diameter of  $10.0\ \mu$  was measured. From the fourth day onwards these large cells gradually disappeared from the circulation though the number of moderately enlarged cells increased. Coinciding with this appearance of large cells there was a corresponding fall in the normal peak, which at the same time moved slightly to the right. It will be noticed also that a few cells of a rather smaller diameter than those normally found were measured, but they were very few in number and the extent of the diminution only ranged over  $5\ \mu$ , whereas the range of the cells larger than normal was up to  $3\ \mu$  and the number of cells involved was considerable.

All the large cells were definitely polychromatic, while the moderately enlarged ones were not uniformly so.

Rabbit R. This animal was bled almost daily for a period of thirty-seven days, the amount of blood removed on each occasion varying. This was usually between 10 and 15 cc., the largest bleeding at any one time being 20 c.c. The total amount removed was 423 c.c.

In this instance the cell distribution curves displayed considerable irregularity and a general movement of the curves to the right, there being but few cells of normal size (Fig. 6). This increase in size was gradual and progressive. Three weeks after the last removal of blood another graph was drawn; this shows that the curve had swung back almost to the normal position. This animal was not killed.

Rabbit O. Exactly the same total amount of blood was removed from this rabbit as was withdrawn from rabbit R, namely 423 c.c., but the bleedings extended over a period of forty-four days and the animal was killed on the forty-sixth day. Further, the blood which was removed was collected in citrated saline solution and then centrifuged, washed, and centrifuged again and the clear supernatant fluid poured off. Distilled water was then added to make the volume equal to the amount of blood removed and the laked cells were then injected into the flank of the animal. It will be seen that the cell distribution curves of this animal show all the changes of the curves of the other two animals of this group (Fig. 7). There is an early appearance of the large polychromatic cells, followed by a general movement of the curve to the right. Later, as the animal appears to accommodate itself to the daily loss of blood, the curve tends to move back to the normal

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position. This animal was killed at the end of the experiment, so there is no curve showing the return to the normal position.

The object of re-injecting the laked blood was to ascertain whether or not it had any influence on the size of the newly-

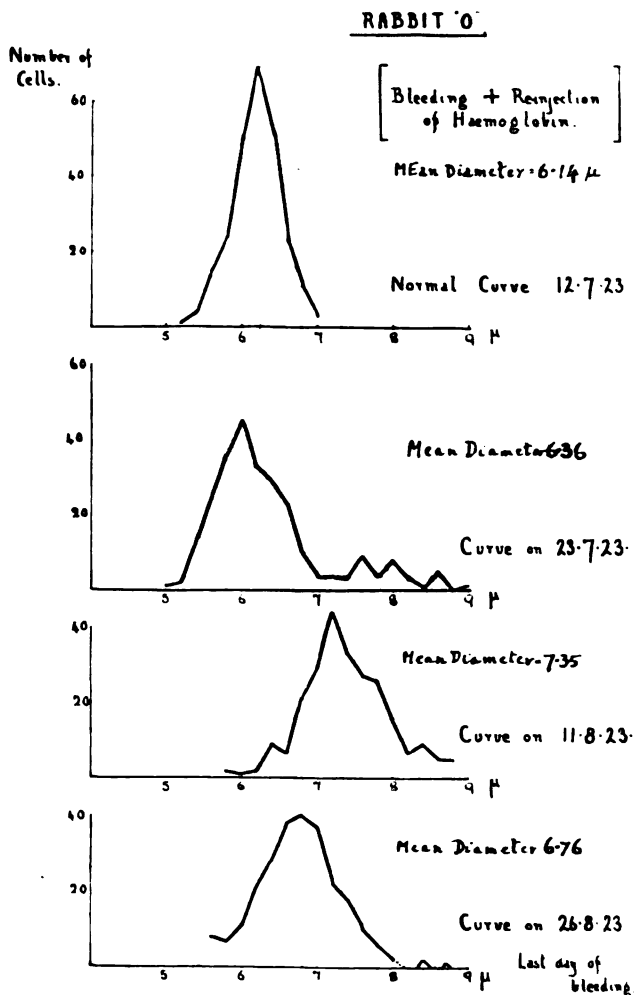


FIG. 7.

Curves showing the effect of Small Repeated Hæmorrhages, with Re-injection of Hæmoglobin.

formed red cells. It is considered that the curves do not show any such effect.

Whereas in man the anæmias resulting from hæmorrhage and sepsis result in the production of small red cells, and the condition known as pernicious or Addison's anæmia in the production of red cells larger than normal, in rabbits it would

seem that the changes in the size of the red cells are identical, whatever the cause of the anæmia. In Fig. 8 curves representing each type of injury are contrasted.

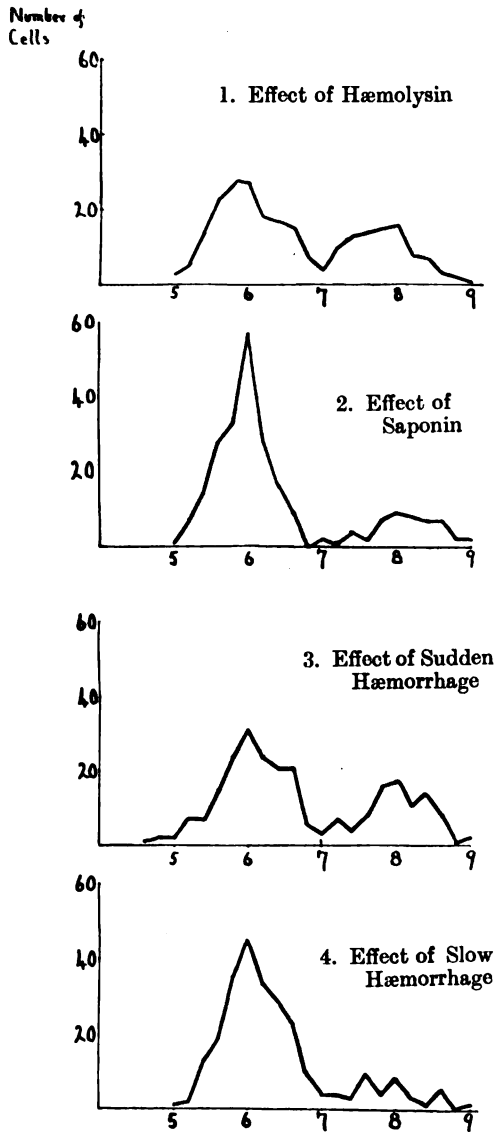


FIG. 8.  
Curves showing the similarity of the effects of  
Hæmolysin, Saponin and Hæmorrhage.

There is at first the production of a few extremely large red cells, the majority of the cells being of normal size. As the animal, however, begins to accommodate itself to the injury the

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majority of the cells become larger in size than the normal, whilst fewer of the extremely large cells are present. If recovery takes place there is a gradual return to the normal size.

### CONCLUSIONS

1. By each of the methods of blood destruction used the same changes were produced in the sizes of the rabbits' red cells.
2. The red cells become larger and the Price-Jones curve moves to the right.
3. With recovery, the red cells return to the normal size, and the curve moves back into the original position.
4. The appearance of the very large polychromatic type of red cell in the hæmorrhage as well as in the hæmolysin and saponin experiments suggests that these large cells are newly-formed cells and not cells damaged in the circulation or during formation.

### APPENDIX

#### METHODS

Enumeration of the red and white cells was made with Burker's modification of the Thoma-Zeiss hæmocyto-meter, and the estimation of the hæmoglobin with a Gowers-Haldane hæmoglobinometer. Normal saline solution was used for the red cell diluting solution and 0.75 per cent. glacial acid in distilled water for diluting the white cells.

Films were made at the same time as the counts, and were fixed and stained in Leishman's stain at once.

The diameters were measured by projecting the image of the microscope field direct, by means of a Zeiss photographic microscope, on to a dead white surface. The positions of the microscope and the white surface were fixed and not altered during the period of the experiment. Thin portions of the films were selected and cells touching each other were not measured.

Instead of outlining the cells in pencil, as described by Price-Jones (1910,<sup>2</sup> 1911<sup>3</sup>), the much-magnified image thrown on the paper was measured directly in two diameters (maximum and minimum) to the nearest  $0.2\ \mu$  by means of a small transparent glass plate, the size of a photographic quarter plate, on which a scale had been drawn in Indian ink. The plate was placed directly over the image of the corpuscle, with the scale along the maximum diameter to be measured. This was read off, and the procedure repeated along the minimum diameter. The mean of the two diameters was taken and recorded. The



results are exactly comparable as the same scale was used throughout.

The scale was made by projecting the image of a slide on which was marked a standard scale with subdivisions into tenths and hundredths of a millimetre. This image was outlined on a sheet of paper. One division of a hundredth of a millimetre was then divided into ten equal parts; this gave measurements in  $\mu$ . One of these subdivisions was then further divided into five equal parts, each one representing  $0.2 \mu$ . This scale was then transferred on to the glass plate.

To avoid errors due to the thickness of the glass the scale, when used for measuring, was on the surface of the glass which was in contact with the paper upon which the image was projected.

A handle of plasticine was fixed on to one corner of the scale in order to facilitate handling.

At the outset of the experiment five hundred cells were measured for each curve, but later only two hundred and fifty were taken, it being found by controlled experiments that the latter gave sufficiently accurate results.

*The actual figures of the blood counts are given in the reprints of this communication.*

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# RODENT ULCER

## ITS INCIDENCE AND TREATMENT

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THE following report, which is based upon 353 cases treated at the hospital, either as in-patients or out-patients within the last twenty years, may be conveniently divided into two parts.

The first of these deals with the sex of the patients, the age of onset, and the situation of the disease, and for this purpose all patients treated at the hospital since 1904 to the present time have been investigated.

The second part deals with the various methods of treatment employed, and includes a comparative analysis of the results achieved. In this section, owing to the difficulty of tracing the earlier cases, only those treated between the years 1913 and 1922 are considered.

In conclusion an attempt is made to arrive at that method of treatment productive of the best results.

### I. INCIDENCE

#### SEX

Of the 353 cases mentioned above, the sex distribution was as follows :—

Males	.	.	.	212	60 per cent.
Females	.	.	.	141	40 „ „

There is clearly no striking difference in the sex incidence, although the males somewhat preponderate.

#### AGE OF ONSET OF THE DISEASE

The age of onset was ascertained in 259 cases. The youngest patient was 22 years old, and the oldest 77 at the time of onset. A consideration of the following diagram (Fig. 1), which illustrates the relation between the frequency of the disease and its age of onset, leaves no doubt that rodent ulcer is most common in the sixth and seventh decade.

THE SITUATION

Of a total number of 320 cases, in which the situation was accurately noted, it was found that 310 ulcers occurred on the face, while in the remaining 10 cases the situation was as follows :—

Back of the hand . . . . .	1
Back of the trunk . . . . .	2
Behind the ear . . . . .	7

On turning to the majority it will be seen from Fig. 2, in which an attempt to illustrate the site of each ulcer has been

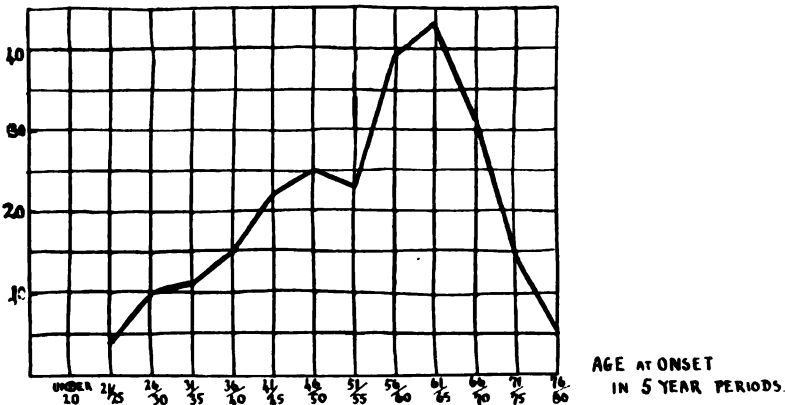


FIG. 1.

Graph to show Age Incidence of 259 Cases of Rodent Ulcer.  
The Cases are grouped into five-year periods.

made, that by far the commonest situation is the nose and adjacent part of the face, excluding, however, the upper lip.

The lower part of the face, with the chin and the lower lip, is only seldom affected, and the same statement is true of the upper part of the forehead and the scalp. This confirms the usual teaching that rodent ulcers commonly lie above an imaginary line joining the angle of the mouth to the lobule of the ear. It is more striking however, to notice that a triangle, bounded by each external canthus, the columella nasi, and the lines joining these points, contains the greater number of lesions. These were found to be distributed equally on the two sides of the face.

MULTIPLE ULCERS

In 17 of the above-mentioned cases, where the site of the lesion was noted, the patient had two or more ulcers. In 14 cases there were two ulcers, and in 3 cases the patient had three

ulcers. These multiple ulcers were sometimes present at the same time and sometimes occurred at intervals of several years.

## II. TREATMENT

For the purpose of investigating the results obtained by the various methods of treatment commonly employed, 270 cases were circularised and definite information regarding the result was obtained from 138 patients. Rather more than half this number appeared for examination in person.

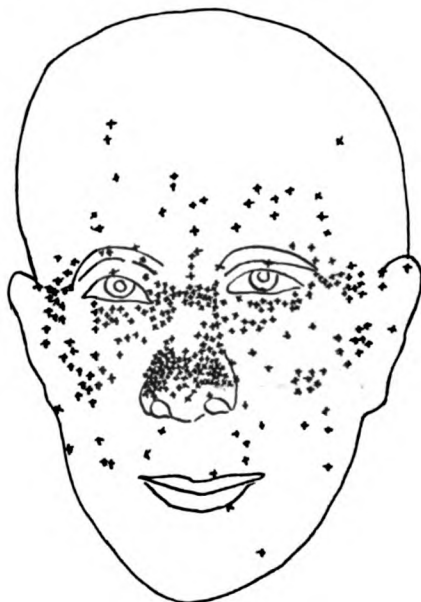


FIG. 2.

Diagram indicating the Site of Origin of the 310 Ulcers occurring on the face.

Among the methods of treatment in common practice, it was found that  $\text{CO}_2$  snow, radium, and x-rays in pastille doses were most generally employed; while in a smaller proportion of cases excision and diathermy were considered more suitable treatment.

It is one of the objects of this report to arrive at a conclusion regarding the efficacy of operative as opposed to non-operative treatment, and for this purpose it is convenient to divide the 138 cases mentioned above into groups :—

1. Those who received as out-patients some form of treatment not requiring a general anæsthetic . . . . 99
2. Those admitted to the wards for operation . . . . 39

Among the factors to be considered as having an important bearing on the general results are the size of the ulcer at the commencement of treatment, the length of history, and the age of the patient. It may be pointed out here that there appears to be no constant relationship between the size of the lesion and the length of history. Of the three factors mentioned above, it will be seen later that probably by far the most important is the size of the ulcer at the commencement of treatment.

In determining the size of the ulcers, the information received from the patient was confirmed in the majority of cases by reference to photographs taken at the time of the patient's first attendance.

#### THE SIZE OF THE ULCER AT THE COMMENCEMENT OF TREATMENT

Information on this point was received in 188 cases, and in order to attain uniformity in classification, they were grouped as follows :—

1. Small ulcers, the size of a sixpenny piece or less.
2. Medium-sized ulcers, the extent of which exceeded that of the first group, but was not larger than a florin.
3. Large ulcers, exceeding the size of a florin.

It is proposed to deal with these groups in turn, indicating the percentage of cures in each. Owing to the relatively large number of cases occurring in the latter years of the series, it is not possible to anticipate the ultimate result in these years. All the cases referred to as cured have remained healed from the cessation of treatment until the present time. It will be seen, therefore, that all the cases recorded as cured in 1922 have remained healed for at least one year, while those in 1918 have remained healed for ten years.

#### SMALL ULCERS

Of the total number of 71 small ulcers treated, it was found that 13 were admitted for operation, either diathermy or excision being performed, and that the remaining 58 were treated in the Light Department by various means.

In the latter group 43 patients were permanently cured, while in the former 9 patients were permanently cured. The relative percentage of successes was therefore as follows :—

	Cured.	Percentage.
58 patients treated by x-rays, radium, etc.	43	75
13 patients treated by diathermy or excision	9	69

Before proceeding with the remaining groups it must be mentioned that, although the size of each ulcer was accurately known in those patients who attended the Light Department, on turning to those in whom operative treatment had been carried out, it was found possible to identify only the small ulcers, owing to want of definite information in the reports. In the following groups, therefore, reference will only be made to cases treated by non-operative means, and the results obtained by operation in the medium-sized and large ulcers will later be considered together.

#### MEDIUM-SIZED ULCERS

In this group 20 patients were treated and 11 were permanently cured.

	Cured.	Percentage.
20 patients treated with x-rays, radium, etc.	11	55

#### LARGE ULCERS

13 patients treated with x-rays, radium, etc.	1	7.6
---	---	-----

Grouping together the medium-sized and large ulcers, treated by operative means, it was found that of 26 cases, 9 were permanently cured. It is probable that the majority of these were ulcers of medium size.

	Cured.	Percentage.
26 patients treated by operation . . . . .	9	34

In general, it is obvious that, whereas treatment by any method is eminently satisfactory in the case of the small ulcer, in the case of the larger ulcer this is by no means the case, and the results are disappointing. Thus in the first group 75 per cent. of the patients were permanently cured, and there is reason to believe that if all cases attended regularly for treatment, which was not the case, this percentage would have been even higher. In the large ulcers the chances of cure by non-operative methods rapidly diminish, and even after prolonged treatment only 8 per cent. are cured. In this group it may be mentioned that several patients attended for periods of a year and more. It will be seen that as regards prognosis medium-sized ulcers occupy a position midway between these extremes.

Turning to a consideration of operative methods, it will be noted that in the case of small ulcers operation was almost, but not quite, as successful as treatment by other methods, the

only important difference being the time necessary to effect a cure in each. From this standpoint only, excision or diathermy under a general anæsthetic is preferable, and it may be said in general that when an ulcer is small at the time when treatment is commenced, the results obtained by any method will be satisfactory.

It has been shown above that treatment of large and medium-sized ulcers in the Out-Patient Department becomes less satisfactory as the ulcer increases in size, and it is in this type of case in particular that operation was generally considered advisable.

Twenty-six cases of large and medium-sized ulcers were admitted to the hospital for operation, and of these 9 were permanently cured, giving a percentage of 84 per cent. As explained above, it has been found impossible in this group to differentiate the large and the medium-sized ulcers, but it is considered probable that most of these were ulcers of the latter type. This result is by no means brilliant, and in considering operations on these patients it must be remembered that they are not without their immediate risks. It was found in the present series that 10 per cent. of the patients succumbed to the operation, death being due to erysipelas, or some other cause directly connected with the operation. It may be mentioned, moreover, that three patients developed panophthalmitis as the result of diathermy applied in the proximity of the eye, which was previously normal although almost invaded by the edge of the ulcer.

A consideration of this evidence leaves little doubt that the size of the ulcer at the time at which treatment is commenced is a factor of great importance in determining results.

#### THE TIME TAKEN TO EFFECT A CURE

Although it is obvious that excision of a rodent ulcer, if successful, produces a cure in far less time than that taken in repeated attendances in the Light Department, at the same time it may be more convenient for the patient to attend the Light Department, and should this be the case it is desirable to know at what time a cure may be expected. In the following diagram, Fig. 8, an inquiry is made into this point, and it is clear that the greater number of cases are cured within the first six months of the commencement of treatment. It is equally clear that after this time the chances of recovery rapidly diminish, until at the end of twelve months they become very slight indeed.

## FAILURE AND RELAPSE

Before considering those cases in which failure was absolute, some attention must be devoted to a small group of 19 cases in which, although a temporary cure was effected after treatment in the Light Department, a relapse followed at no distant date. Of these 19 ulcers, it should be noted that 12 were small at outset of treatment, 6 were medium-sized, and 1 was large. The most significant fact in relation to each case in this group is that, without a single exception, treatment was either completed in less than three months, or continued for periods of more than a year. It has already been pointed out that treatment in the Light Department for periods exceeding six months

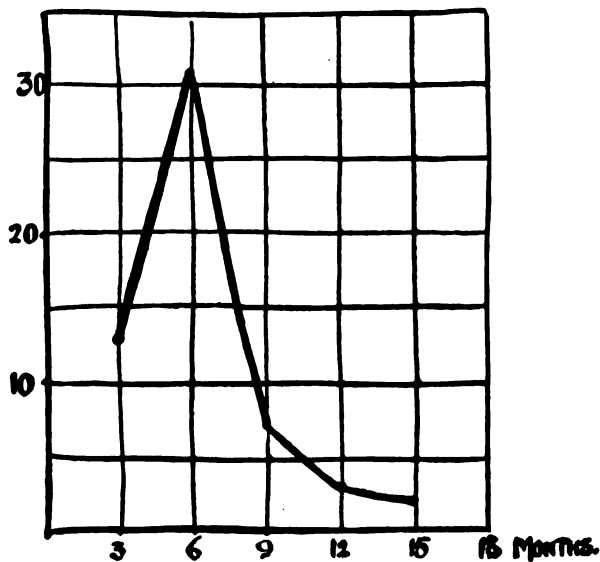


FIG. 3.

Graph to show Duration of Treatment in 56 Cases from the Light Department, in which a cure resulted.

is unlikely to meet with success, so relapses after long-continued treatment in chronic cases cannot be considered surprising. Small ulcers, on the other hand, heal with great readiness after adequate treatment, and, in the 12 cases referred to above, failure was probably due to insufficient treatment in the first instance.

The necessity of prolonging for a sufficient period the treatment of every case of rodent ulcer, in which the lesion is small at the outset of treatment, is further emphasised by a



consideration of those cases in which treatment was a complete failure.

It has been mentioned that of the 58 small ulcers treated by x-rays, radium, and CO<sub>2</sub> snow, 43 were permanently cured and 12, although at first cured, later relapsed. In the remaining three cases treatment was unsuccessful; in the first of these the patient was only treated on three occasions, in the second treatment was discontinued after 10 days, while in the third, although the patient attended for 12 months, the lesion became progressively worse.

On turning to the medium-sized ulcers similar causes of failure are to be found; for, of the three cases in this group, failure in two was almost certainly due to insufficient treatment, while in the third patient, whose age was 84, the ulcer, a large and chronic lesion of 20 years' history, was unlikely to be affected by any treatment less than excision.

In the last group, that of the large ulcers, of a total of 18 cases 11 completely failed to heal.

The ulcer in every case was one of several years' history, and the patient was in most cases over 70 years of age when treatment was commenced. In one case the patient was 84, and although there can be no doubt that the average age of the patient with these ulcers is somewhat higher than that of the majority, it is probable that the size of the ulcer is a more important factor in determining the success or otherwise of the treatment adopted. These cases, being unsuitable for non-operative treatment, are handed over to the surgeon, and the age of the patient now becomes of importance when the question of a general anæsthetic has to be considered.

A careful consideration of these facts leaves little doubt that the treatment of rodent ulcer in its early stages is extremely satisfactory, whatever the method used, and there is reason to believe that the results would be even more satisfactory if the treatment adopted were thoroughly and efficiently carried out during the six months subsequent to the commencement of the treatment. It is true that there is a small percentage of cases, which will not respond in the usual way, and as soon as it becomes evident that non-operative treatment is leading to no improvement, it should be at once abandoned and the ulcer excised. It is not wise to delay excision for more than six months after the commencement of treatment, for it has been shown above that the chances of a permanent cure after this time gradually decline.

As soon as an ulcer reaches the stage at which it can be called large, it presents to the surgeon a very serious problem.

Only the very widest excision, with possibly the loss of an eye or the removal of part of the superior maxilla, will offer any hope of limiting the spread of the disease.

We wish to thank the members of the staff, who have kindly given us permission to investigate the cases which have been under their care.

#### CONCLUSIONS

(1) Rodent ulcer occurs rather more frequently in men than in women.

(2) It may occur at any age over 20, but is most frequent between the ages of 60 and 65.

(3) Although it may affect any part of the body, it more often appears on the nose and the adjoining parts of the face, where it may possibly be related to some peculiarity of the sebaceous glands in this region. It is suggestive that in this situation the ducts of the glands are more exposed, and are distinguished by the relatively large size of their apertures.

(4) Treatment in the early stage of the disease is very satisfactory whatever the method employed. Excision is unnecessary at this stage, but should be resorted to as soon as it becomes evident that non-operative treatment is unavailing.

(5) Treatment in the late stage is far from satisfactory; sufficiently widespread excision in these cases may be impossible and diathermy is then the only alternative.

(6) In the neighbourhood of the eye diathermy should be used with greatest care, as accidental sparking on to the globe of the eye may be followed by disastrous results.

(7) In the 138 cases, which it was possible to trace, no instance has occurred in which the ulcer has shown malignant characteristics other than those of a local nature.

APPENDIX I

Summary of 99 cases treated in the Light Department.

Year.	Number of cases.	Information obtained.	Cured.	Not cured.	Relapsed.	Fresh ulcer.
1913	22	9	6	1	2	0
1914	26	9	4	4	1	0
1915	27	13	9	4	0	0
1916	9	5	2	1	2	0
1917	22	10	6	3	1	0
1918	19	9	4	2	3	0
1919	22	8	6	0	2	1
1920	6	6	4	1	1	1
1921	7	4	3	0	1	0
1922	29	26	16	4	6	0
	189	99	60	20	19	2

Table showing the size of the ulcer and its relation to healing.

Size.	Number.	Healed.	Relapsed.	Not cured.
Small . . . . .	58	43	12	3
Medium . . . . .	20	11	6	3
Large . . . . .	13	1	1	11

APPENDIX II

Summary of the cases admitted to the Surgical Wards.

The result is known in 39 cases out of the 50 cases operated upon.

1. EXCISION . . . . .	23
2. EXCISION and DIATHERMY . . . . .	6
3. DIATHERMY . . . . .	9
	39

1. EXCISION. 23 cases . . . . .	Healed 16	}	HEALED 19
	Unhealed 6		
	Died 1		
2. EXCISION combined with DIATHERMY. 6 cases	Healed 1	}	UNHEALED 15
	Unhealed 3		
	Died 2		
3. DIATHERMY. 9 cases . . . . .	Healed 2	}	DIED 5
	Unhealed 6		
	Died 1		
			39

One other case died in the ward after operation, but the details of the operation are not given in the report.

## THE HAGEDORN-JENSEN METHOD OF ESTIMATING BLOOD SUGAR

By W. W. PAYNE, M.B., Parson's Research Fellow, Guy's Hospital.

HAGEDORN and Jensen of Copenhagen have recently published <sup>1</sup> a new method of estimating blood sugar, which has several advantages over those at present in use.

As there is apparently no working description of this method in English it was thought that a short account might be useful.

The principle is to precipitate the blood protein by means of zinc hydrate; to oxidise the sugar in the filtrate by potassium ferricyanide, and to estimate the residual ferricyanide by taking advantage of its power to liberate iodine from iodides.

### SOLUTIONS REQUIRED

#### (A) *For protein elimination.*

1. N/10 NaOH.
2. 0.45% ZnSO<sub>4</sub>.

*Note.*—If these solutions are left standing for some time the "blank" value will increase. It is best to make them up fresh every week from a stock solution of normal or twice normal NaOH and a solution of 45 gms. of zinc sulphate in 100 c.c. water.

#### (B) *For sugar estimation.*

##### 1. Alkaline ferricyanide solution.

1.65 gms. of twice re-crystallised potassium ferricyanide; 10.6 gms. of sodium carbonate which has been heated to redness; distilled water to one litre.

This solution should be kept in the dark. It will then last a month or two without much deterioration.

##### 2. Potassium iodide-zinc sulphate solution.

Potassium iodide	.	5 gms.
Zinc sulphate	.	10 gms.
Sodium chloride	.	50 gms.
Water to	.	200 c.c.

This solution sometimes tends to liberate free iodine. This may be avoided by adding the potassium iodide to a small amount of the stock solution when required or by keeping a piece of metallic zinc in the solution. If free iodine occurs it can be removed almost completely by filtering through thick

filter paper. Small amounts of free iodine are allowed for in the blank.

3. Acetic acid solution.

Glacial acetic acid.	8 c.c.
Water to	100 c.c.

The glacial acetic acid should be iron-free.

4. Starch solution.

1 gm. soluble starch.
100 c.c. saturated sodium chloride solution.

5. N/200 sodium thiosulphate solution.

This solution will keep only for a few days, and it is best to keep a stock solution containing 25 gms. to the litre. 5 c.c. of this diluted to 100 c.c. is approximately N/200. The stock solution must be kept in a blue bottle in the dark. These solutions need not be very accurate.

6. N/200 Potassium iodate solution for standardising the sodium thiosulphate. (This must be accurate.)

Pure potassium iodate	0.8566 gms.
Water to	2000 c.c.

This solution keeps well.

#### METHOD

Into a test-tube ( $\frac{1}{2}$  by 6) 1 c.c. N/10 NaOH and 5 c.c. of .45 per cent.  $\text{ZnSO}_4$  are placed. 0.1 c.c. of blood is obtained in an accurate capillary pipette graduated .05 and .1 c.c.,\* and is blown out into the test-tube. The pipette is then washed out twice with the precipitating solution. If it is suspected that the blood sugar is much over 0.3 per cent., only .05 c.c. of blood should be used. The tube is then placed in a boiling water bath for three minutes. A coarse grey coagulum is formed, leaving a clear colourless fluid. At this point it is possible to leave the estimation for some twenty-four to forty-eight hours without fear of glycolysis.

The contents of the test-tube are next filtered into a large boiling tube (1" by 6") wet cotton wool being used instead of filter paper. The cotton wool used should be absorbent and should be only lightly packed into the funnel. It is best to place a small piece of cotton wool in the neck of the funnel and then a somewhat larger piece on top; the diameter of the filter bed need not be greater than that of a shilling. The test-tube and filter funnel are then washed out twice with 3 c.c. of distilled water. It is important that the filtrate be quite clear.

\* Messrs. Hawksley & Sons make a suitable pipette.

Two c.c. of the ferricyanide solution are then added to the filtrate and the mixture placed on the water bath for fifteen minutes. The sugar reduces the ferricyanide to ferrocyanide, which is precipitated as a zinc compound by the zinc sulphate present. There is no danger of back oxidation of the ferrocyanide even after several hours. After cooling, 3 c.c. of the potassium iodide-zinc sulphate solution, and 3 c.c. of the acetic acid solution and two drops of the starch solution are added and the mixture titrated with N/200 thiosulphate until the blue colour is just discharged. The burette used should be capable of being read to 0.01 c.c.

A complete "blank" estimation should be performed at the same time by using the mixture of 1 c.c. N/10 NaOH and 5 c.c. 0.45 per cent.  $\text{ZnSO}_4$  and treating it the same as if the blood had been added.\*

The reason for this is that there are always some substances present capable of reducing the potassium ferricyanide and thus simulating glucose. There should not be a big difference between the "blank" value and the value obtained by titrating 2 c.c. of the ferricyanide solution mixed with 12 c.c. of water, 3 c.c. of the potassium iodide-zinc sulphate solution and 3 c.c. of the 3 per cent. acetic acid solution. If there is, it is due either to impurities in the reagents, to the precipitating solutions being too old, or to the distilled water. There is no need to titrate the ferricyanide solution every time, as the value varies very little from week to week.

#### STANDARDISATION OF THE THIOSULPHATE SOLUTION.

Ten c.c. of the N/200 potassium iodate are placed in a beaker, and a very small crystal of potassium iodide added and then one drop of a dilute hydrochloric acid solution. The thiosulphate is then run in from a burette until the yellow colour of the iodine is almost gone. A few drops of the starch solution are then added and the titration completed. A second titration should be made, adding the thiosulphate required previously as quickly as possible, and then completing the titration as before. A third titration is usually necessary, as the first result is often low.

#### CALCULATION

The volume of thiosulphate solution used for the "blank" and the blood determinations are now corrected to N/200. If the "blank" equals 2.00 (the theoretical value) the percentage of

\* Some difficulty may be found in filtering the "blank" owing to some of the precipitate passing the cotton-wool filter; this, however, may be neglected, as the presence of zinc hydrate in the filtrate makes no difference to the value ultimately obtained.

# ESTIMATING WITH BLOOD SUGAR 243

sugar can be read straight from the table; otherwise the blank titration is subtracted from 2·00, and the result added to the blood determination and the sugar percentage read off from the table as before; *e. g.* :

Blank . . . . . 1·91 c.c.  
 " Blood " titration . . . 1·10 c.c.  
 2·00 - 1·91 = . . . . . 0·09 c.c.  
 1·10 + 0·09 = . . . . . 1·19 c.c.

This corresponds on the Table to 143 mg. sugar, *i. e.* 0·143 per cent., if 1 c.c. blood was used.

C.c. N/200-sodium thiosulphate—mg. glucose.

	0	1	2	3	4	5	6	7	8	9
0·0	0·385	0·382	0·379	0·376	0·373	0·370	0·367	0·364	0·361	0·358
0·1	0·355	0·352	0·350	0·348	0·345	0·343	0·341	0·338	0·336	0·333
0·2	0·331	0·329	0·327	0·325	0·323	0·321	0·318	0·316	0·314	0·312
0·3	0·310	0·308	0·306	0·304	0·302	0·300	0·298	0·296	0·294	0·292
0·4	0·290	0·288	0·286	0·284	0·282	0·280	0·278	0·276	0·274	0·272
0·5	0·270	0·268	0·266	0·264	0·262	0·260	0·259	0·257	0·255	0·253
0·6	0·251	0·249	0·247	0·245	0·243	0·241	0·240	0·238	0·236	0·234
0·7	0·232	0·230	0·228	0·226	0·224	0·222	0·221	0·219	0·217	0·215
0·8	0·213	0·211	0·209	0·208	0·206	0·204	0·202	0·200	0·199	0·197
0·9	0·195	0·193	0·191	0·190	0·188	0·186	0·184	0·182	0·181	0·179
1·0	0·177	0·175	0·173	0·172	0·170	0·168	0·166	0·164	0·163	0·161
1·1	0·159	0·157	0·155	0·154	0·152	0·150	0·148	0·146	0·145	0·143
1·2	0·141	0·139	0·138	0·136	0·134	0·132	0·131	0·129	0·127	0·125
1·3	0·124	0·122	0·120	0·119	0·117	0·115	0·113	0·111	0·110	0·108
1·4	0·106	0·104	0·102	0·101	0·099	0·097	0·095	0·093	0·092	0·090
1·5	0·088	0·086	0·084	0·083	0·081	0·079	0·077	0·075	0·074	0·072
1·6	0·070	0·068	0·066	0·065	0·063	0·061	0·059	0·057	0·056	0·054
1·7	0·052	0·050	0·048	0·047	0·045	0·043	0·041	0·039	0·038	0·036
1·8	0·034	0·032	0·031	0·029	0·027	0·025	0·024	0·022	0·020	0·019
1·9	0·017	0·015	0·014	0·012	0·010	0·008	0·007	0·005	0·003	0·002

## RESULTS

The accuracy of this method is fully equal to that of any of the other methods. The following figures of duplicates and known amounts of sugar were obtained in the course of ordinary routine estimations :

Duplicate (a).

Mr. W. :—

11.15 p.m. Blood from right ear. Blood sugar 125%.  
 11.20 p.m. „ „ left ear. „ „ 124%.  
 6.20 a.m. „ „ left ear. „ „ 122%.  
 6.23 a.m. „ „ right ear. „ „ 119%.

Duplicate (b).

Miss P. :—

Blood from finger each time.

10.36 a.m. Blood sugar ·105%.

10.46 p.m. „ „ ·105%.

10.51 a.m. „ „ ·106%.

10.59 a.m. „ „ ·107%.

(c) ·097 mg. sugar added instead of blood. Sugar found :  
·095 mg., ·093 mg., ·092 mg.

(d) Compared with Folin and Wu's method (modified to use ·2 c.c. blood), the following results were obtained :

*Folin and Wu.*

·262 per cent.

·307 „

*Hagedorn and Jensen.*

·268 per cent.

·306 „

As regards time, a single estimation takes about the same time as McLean's method (say forty minutes), while Folin and Wu's method takes about thirty minutes. If many estimations have to be made, there is no limit to the number that can be put into the same batch, and the authors state that eighteen an hour can be done. Without assistance I cannot perform more than ten to twelve an hour, but much time could be saved by the help of even a relatively untrained assistant, as at least a third of the time is spent collecting and preparing apparatus. In the Folin-Wu method about 10 to twelve can be put into one batch, which then takes about an hour. The advantages of the Hagedorn-Jensen method are thus :

- (1) Speed.
- (2) Accuracy.
- (3) No special apparatus is required.
- (4) The estimation can be left at almost any point for several hours, without loss of accuracy.

The sole disadvantage is the lack of stability of some of the solutions.

In conclusion, my thanks are due to Lieut.-Commander F. Maxse, R.N., for supplying me with an excellent translation of the original German paper, and also to Dr. J. H. Ryffel for the generous way he has permitted me to use his laboratory and apparatus.

#### REFERENCE

- <sup>1</sup> H. C. Hagedorn and B. N. Jensen : *Biochemische Zeitschrift*, Vol. 135, October, 1922.



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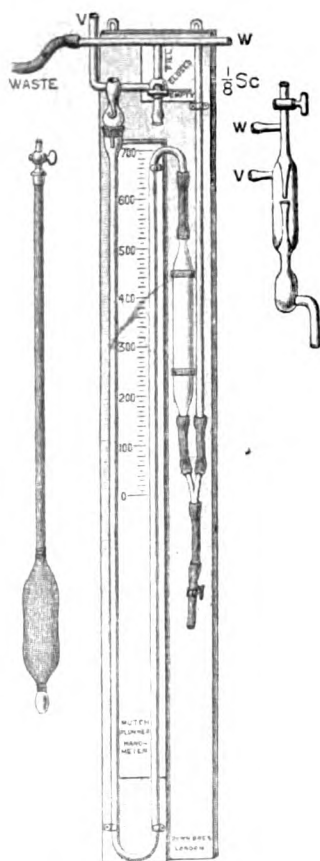
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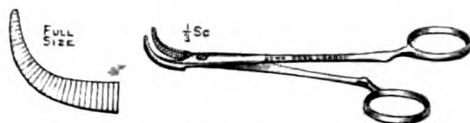
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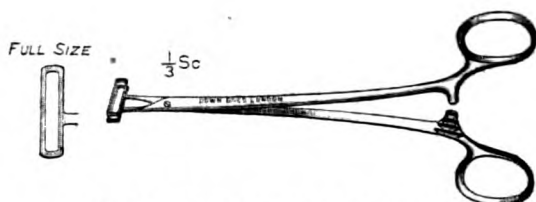
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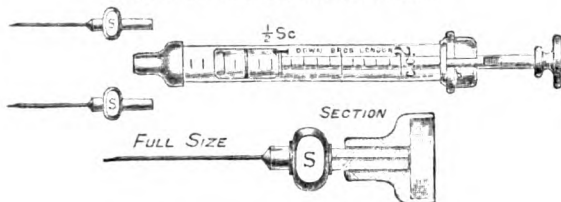
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## THE INVESTIGATION OF THE DUODENAL CONTENTS AND BILE IN MAN

By J. F. VENABLES, M.D., Assistant Physician to New Lodge Clinic, and  
F. A. KNOTT, M.D., Pathologist to New Lodge Clinic and Clinical  
Assistant Medico-Neurological Clinic, Guy's Hospital.

IN 1917 Meltzer<sup>1</sup> discovered that the injection of a 25 per cent. solution of magnesium sulphate into the duodenum of animals was followed almost immediately by an abundant flow of bile. He showed that the flow of bile depends on the fact that when the magnesium sulphate solution is brought into contact with the duodenal mucosa a reflex is produced, which results in contraction of the gall-bladder and bile ducts and relaxation of the sphincter of the common bile duct, so that bile is discharged into the duodenum. Lyon,<sup>2</sup> carrying out investigations with an Einhorn tube, confirmed these findings in man, and claimed that three different kinds of bile were successively obtained—(1) from the common duct, (2) from the gall-bladder and (3) from the liver. The "common duct bile" was stated to have the consistence of thin syrup, and to vary in amount from 5 to 10 c.c.; "the gall-bladder bile" was of darker colour and thicker in consistence, and varied in quantity from 25 c.c. to 100 c.c.; the "liver bile" was pale yellow in colour and much more fluid in consistence.

The following paper is a review of 100 consecutive examinations in which the duodenal and gall-bladder contents were investigated; seventy-four of the specimens were obtained from cases investigated at New Lodge Clinic, and the remaining twenty-six were from cases under the care of Dr. A. F. Hurst at Guy's Hospital.

### *Technique*

The specimens were collected by means of an ordinary Einhorn tube introduced into the duodenum. No food or drink had been taken by the patient during the preceding nine hours. The tube was sterilised and swallowed, and the stomach was then emptied by suction with a "record" syringe. It was then washed out with sterile water to prevent, as far as possible, the passage into the duodenum of organisms or cells swallowed with the saliva. The tube was then slowly introduced further,

while the patient lay curled up on his right side and slightly over on to the face. The time required for the tube to enter the duodenum was anything from ten minutes to one hour, but generally less than half an hour was sufficient. In achlorhydria the time elapsing before entry into the duodenum occurs is almost invariably short, owing to the permanently relaxed condition of the pyloric sphincter.

During the period in which the present series of cases was being investigated, failure to obtain entry into the duodenum only occurred twice; both these cases showed well-marked gastropptosis when examined with the x-rays.

Although the presence of the tube in the duodenum was occasionally verified by x-ray examination, this is not really necessary, as the moment when entry into the duodenum occurs can be easily determined by simpler means. As long as the tube is in the stomach suction with a syringe causes the aspiration of small quantities of fluid, which evolves large bubbles in the barrel of the syringe and which is hardly ever bile-stained: this fluid, except in cases of achlorhydria, gives an acid reaction to litmus paper. Directly the duodenum has been entered, the physical character of the fluid changes; the fluid aspirated is no longer mixed with large bubbles, but consists of a fine froth, generally slightly bile-stained, which invariably gives a neutral or alkaline reaction to litmus.

As soon as the duodenum is entered, a specimen of the contents is removed by a sterile "record" syringe and transferred to a sterile container. The duodenum is then washed out with sterile water before introducing about 10 c.c. of a sterile 25 per cent. solution of magnesium sulphate. Within a minute or two a copious flow of bile is almost invariably obtained, and a specimen of this is removed by a second sterile syringe. In no single instance in this series of 100 cases were we able to satisfy ourselves that the three consecutive types of bile, described by Lyon, were present.

#### *Classification of Cases and Results*

The cases under review fall into three main groups. The first group is composed of cases of gall-bladder disease; this group numbers 29. It has been sub-divided under two headings: (1) cases of proved gall-bladder disease; (2) cases diagnosed clinically as cholecystitis or cholelithiasis, but not operated on and treated medically. The second group consists of eighteen cases of Addison's anæmia and of subacute combined degeneration of the spinal cord. The third group, fifty-one in number,

cannot be classified under any definite heading, and has been labelled "other diseases." Included in this last group are a few cases examined simply as controls. There were five cases of appendicitis, three of which had been sent with the diagnosis of gall-bladder disease; the diagnosis was subsequently changed to appendicitis, and in each case this was confirmed by operation and the gall-bladder was found to be normal. Among the remaining cases there were eight of neurasthenia, eight of rheumatoid arthritis and three of gastric or duodenal ulcer.

The microscopic and bacteriological findings have been grouped under five headings: (1) leucocytes; (2) cholesterol crystals; (3) infection with *Streptococcus longus*; (4) infection with coliform bacilli; (5) no infection, either non-pathogenic organisms, such as *Staphylococcus albus* or spores, being present, or the specimens remained completely sterile on cultivation. With one exception the pathogenic organisms obtained proved to be either streptococci or coliform bacilli.

In order to compare the relative frequency of infection in the different types of gastric secretion, the cases have been further divided into five groups in accordance with Bell's<sup>3</sup> classification of types of gastric secretion: (1) achlorhydria; (2) low normal; (3) normal; (4) high normal; (5) hyperchlorhydria.

#### NOTES ON LABORATORY FINDINGS

When considering a case series of this kind it is essential briefly to mention the main points of interest in the laboratory methods adopted and the microscopical appearances from which deductions have been made.

Among the normal cases it must be noted that the centrifuged deposits obtainable from the duodenal contents and gall-bladder bile were always extremely small and, if preliminary gastric lavage had been satisfactory, they usually contained only mucoid material and isolated columnar cells. Squamous epithelial cells and food débris were rarely found, and, in compiling this record, all those specimens which did contain these two elements were discarded as being possibly contaminated from the upper alimentary tracts. Also it is probable that, by this elimination, the reliability of the bacteriological results has been greatly increased.

On rare occasions one found in specimens from normal people a few isolated leucocytes, but the positive presence of leucocytes was reported only when they occurred as frequently as about five per field under the one-sixth inch objective.

Stained films from normal specimens usually contained a considerable number of bacterial forms, but the majority of these showed signs of partial disintegration and abnormal staining reactions, suggesting that few if any were viable, a supposition well borne out by the high percentage of normal specimens which, on repeated cultivation, remained quite sterile. It seems, in fact, that a duodenal specimen collected from a normal person by the technique described is practically cell free and, as might be expected if the gastric acidity is normal, is sterile or contains only the most resistant types of bacteria.<sup>4</sup>

Turning next to the various pathological conditions, a few points in microscopical appearance must be mentioned. We have already referred to the presence of leucocytes. Our findings in connection with detached columnar epithelial cells are in agreement with those of Loeber,<sup>5</sup> who recently reported examination of a number of similar specimens. In inflammatory conditions of the duodenum and biliary passages, one frequently sees groups of such epithelial cells apparently detached *en bloc*, and this seems particularly to occur in specimens obtained after the administration of magnesium sulphate, suggesting that this solution tends to detach the already weakened epithelium but hardly affects it when in its normal state. Cells, epithelial or leucocytic, actually derived from the biliary passages frequently show deep coloration by bile pigment, providing a definite clue as to their origin.

In examining the deposits for cholesterol crystals, apart from immediate centrifugalisation, a second portion was allowed to remain for some time at 37° C. with occasional shaking, so that every opportunity might be given for the crystals to re-dissolve. It was also noted that in no case did a normal specimen of diluted alkaline gall-bladder bile obtained after administration of magnesium sulphate deposit any appreciable number of cholesterol crystals, even after standing for two days at room temperature. As in the case of leucocyte detection, only those specimens were reported as containing cholesterol crystals, in which the typical notched plates were readily demonstrable and permanently present. Other crystals, which may appear in the duodenal and gall-bladder contents, are phosphates, yellow rhombic plates of bilirubin, and, in the latter specimens, rectangular crystals of magnesium sulphate; but all these are easily distinguishable from cholesterol.

For bacteriological examination, each specimen was directly plated on to bile-salt agar and blood agar and incubated and sub-cultivated aerobically at 37° C. For the results here recorded, reinforcement methods were not employed, as it



was considered desirable to report an organism as present only when, in plates made directly from the duodenal contents, it was culturable in considerable numbers. In each case the appearances of stained films were in accord with the plate findings. In the above bacteriological records it should be remembered that, unless otherwise stated, each organism mentioned was abundantly present, and that, if potentially pathogenic, its significance must be considered accordingly. The sterility of specimens was carefully confirmed, broth as well as plate cultures being made in these instances.

### *Infection*

The following table shows the percentage of cases with infection of either the duodenal or gall-bladder contents in the five types of gastric secretion.

	Number of cases.	Number infected.	Percentage infected.
(1) Achlorhydria . . . . .	34	28	82.4
(2) Low normal . . . . .	7	1	14.3
(3) Normal . . . . .	33	9	27
(4) High normal . . . . .	15	4	26.6
(5) Hyperchlorhydria . . . . .	11	4	36.4
(6) (2), (3), (4), & (5) together . . . . .	66	18	27.3

It will be seen that the duodenum or gall-bladder is infected three times as often in achlorhydria as in patients with free hydrochloric acid in their gastric contents. If Addison's anæmia, in which achlorhydria and infection are always present, and if gall-bladder disease, in which infection might be expected regardless of the type of secretion, are excluded, the percentage of infection in the group of "other diseases" works out as follows :—

	Number of cases.	Number infected.	Percentage infected.
(1) Achlorhydria . . . . .	9	6	66.6
(2) Low normal . . . . .	5	Nil	Nil
(3) Normal . . . . .	19	4	21
(4) High normal . . . . .	12	2	16.6
(5) Hyperchlorhydria . . . . .	4	Nil	Nil
(6) (2), (3), (4), & (5) combined . . . . .	40	6	15

This table also shows that the incidence of infection in achlorhydria is more than four times as high as in all the other cases. On ascertaining the nature of the cases which give the rather

high percentage of infection in Groups 3 and 4, we find that four of the six are cases of rheumatoid arthritis, one a case of post-operative diarrhoea, in which part of the small intestine had been resected on two occasions, and one a case of ascending colon stasis. The six cases of infection in the group of achlorhydria fall into no definite group; there was one case of rheumatoid arthritis, the remaining five showed no signs of organic disease.

These figures confirm the findings of one of us (F. A. K.)<sup>4</sup> in regard to the bactericidal power of the gastric secretion.

### *Gall-Bladder Disease*

There were sixteen specimens from cases of proved gall-bladder disease. Of these, six were from cases of gall-stones subsequently removed at operation. There was one further case of gall-stones, in which no operation was performed, but a gall-stone was clearly visible with the x-rays. The remaining cases comprise nine of cholecystitis and one of mechanical obstruction of the cystic duct due to kinking, all confirmed at operation.

(1) *Leucocytes*.—Leucocytes were present in the gall-bladder contents in eight cases, or 50 per cent., compared with only three out of fifty-seven cases, or 5·8 per cent., among the group of "other diseases."

(2) *Cholesterol crystals*.—Cholesterol crystals were present in the gall-bladder contents of eight cases, or 50 per cent. In no single instance were cholesterol crystals found in the fifty-one cases of "other diseases." Although in several cases leucocytes and crystals were present in the same specimen, the identical percentages obtained do not signify that all contents showing cholesterol crystals also contained leucocytes, the identical percentages being a coincidence.

In the six cases of gall-stones proved by operation, cholesterol crystals were present in five gall-bladder contents, or 83·3 per cent. Three cases showed the presence of crystals, but no gall-stones were found at the operation. Two of the gall-bladders in these three cases showed very old and chronic changes due to cholecystitis; the third gall-bladder had been drained at a previous operation.

(3) *Streptococcus longus*.—In none of the sixteen cases of gall-bladder disease was a *Streptococcus longus* isolated either from the duodenal or gall-bladder contents.

(4) *Coliform Bacilli*.—Coliform bacilli were present in the gall-bladder contents of seven patients, or in 43·7 per cent. of cases, and one specimen gave a strong growth of *B. proteus* in both the duodenal and gall-bladder contents. In contrast with

this the group of "other diseases" shows the presence of coliform bacilli in only eleven gall-bladder contents, or 21·6 per cent., and six of these specimens were obtained from cases associated with achlorhydria.

(5) *Non-infected bile*.—The remaining eight specimens either contained non-pathogenic organisms or remained sterile on cultivation. The gall-bladders in six of these cases were examined bacteriologically and microscopically after operation; in each case quite definite microscopic evidence of old inflammation was found, but no evidence of active bacterial invasion of the walls could be seen, and the cultures obtained directly from the gall-bladder walls and from the bile immediately after operation, remained sterile.

#### " Probable " Gall-Bladder Disease

There were ten cases of "probable" gall-bladder disease, in which the diagnosis was considered established, but no operation was performed. Thirteen specimens were examined, as in one case three specimens were taken, and in a second two specimens; in each case the first specimen was obtained before treatment was commenced.

(1) *Leucocytes*.—Leucocytes were present in the gall-bladder contents in ten instances; this gives a percentage of 27·6 as against 5·8 in the group of "other diseases."

(2) *Cholesterol crystals*.—Cholesterol crystals were present in the gall-bladder contents in seven instances, the percentage being 53·4 as against *nil* in the group of "other diseases."

(3) *Streptococcus longus*.—In none of the thirteen cases was a *Streptococcus longus* grown either from the duodenal or gall-bladder contents.

(4) *Coliform bacilli*.—Coliform bacilli were present in eight of the specimens of gall-bladder bile, the percentage being 61·5 as against 24·6 found in the group of "other diseases."

(5) *Non-infected bile*.—One specimen gave a growth of *Staphylococcus aureus*. Three of the sterile specimens were obtained from cases in which the examination was repeated after treatment with large doses of urotropine had been carried out, the first examination having shown that the gall-bladder contents were heavily infected. In only one case, therefore, was no pathogenic organism found before treatment was begun, and the actual case percentage of infection was 90.

*Addison's Anæmia*

Eighteen cases of Addison's anæmia or subacute combined degeneration of the cord were investigated; achlorhydria was present in all.

(1) *Leucocytes*.—Leucocytes were present in the duodenal contents in six cases, or 30 per cent., the percentage in the group of "other diseases" being 4.

(2) *Cholesterol crystals*.—No cholesterol crystals were found in either the duodenal or gall-bladder contents in these cases.

(3) *Streptococcus longus*.—A *Streptococcus longus* with hæmolytic properties was grown from the duodenal contents in fourteen specimens as against *nil* in both the other groups of cases. All the six specimens, which failed to yield a streptococcus, were from cases which had previously been treated by oral administration of large doses of dilute hydrochloric acid, though no acid was being taken actually at the time when the tests were carried out. In two of these cases a *Streptococcus longus* was obtained before treatment; after treatment for some months the duodenal contents of one was completely sterile and that of the second contained *B. coli*, but no streptococci.

These findings strengthen the view of Hurst that Addison's anæmia is due to the absorption of hæmolytic toxins from the intestine, where they are formed by the action of streptococci, which reach the intestine owing to the loss of the normal antiseptic action of the gastric juice caused by the achylia always present in this disease. In no single instance was a hæmolytic streptococcus recovered from the duodenal contents of other cases in this series; in fact in only one case was a growth of *Streptococcus longus* obtained, and this proved to be definitely non-hæmolytic. It is worthy of note that in fifteen of these other cases achlorhydria was present. In addition to the present series twelve further cases of Addison's anæmia under the care of Dr. A. F. Hurst have all yielded a *Streptococcus longus* from the duodenal contents.

(4) *Coliform bacilli*.—Coliform bacilli were present in thirteen cases, or 65 per cent., the group of "other diseases" showing eleven infected contents, or 22 per cent. Of these eleven, five, or 45 per cent. had achlorhydria. It may therefore be assumed that the presence of *B. coli* in the duodenal contents in cases of Addison's anæmia is probably due simply to the achlorhydria and is of little significance compared with the presence of achlorhydria.

*Other Diseases*

(1) *Leucocytes*.—In the fifty-one specimens obtained from this group leucocytes were found in the duodenal contents in two cases. In one case there was severe pyorrhœa associated with achlorhydria, and the second was a case of rheumatoid arthritis.

Three specimens of gall-bladder bile contained leucocytes. One of these specimens was from the case of rheumatoid arthritis mentioned above; the second was from a case of alcoholic gastritis, and the third was from another case of rheumatoid arthritis.

(2) *Cholesterol crystals*.—No cholesterol crystals were found in duodenal contents or gall-bladder bile in this group of cases.

(3) *Streptococcus longus*.—None of the fifty-one specimens of duodenal contents obtained showed infection with *Streptococcus longus*.

(4) *Coliform bacilli*.—In nine cases both the duodenal contents and gall-bladder bile showed infection with coliform bacilli. Four of these were cases of rheumatoid arthritis. In three cases no organic disease was present, but all these three had achlorhydria. The other two specimens were from the case of severe pyorrhœa associated with achlorhydria mentioned above and from a case with a gastric ulcer. Two specimens showed infection of the duodenal contents only, one being from a case of rheumatoid arthritis and the other from a case of ascending colon stasis. In two instances in this group the gall-bladder bile alone showed infection. One specimen was from a case of alcoholic gastritis and the second from a case of neurasthenia.

*Conclusions*

It would seem from the results obtained that it is possible to obtain valuable information by the duodenal tube in cases of gall-bladder disease and in certain other diseases where an infection of the upper gastro-intestinal tract is present, notably in Addison's anæmia.

The investigations have fully borne out the results claimed for the action of magnesium sulphate when injected into the duodenum. In almost every case the specimen obtained after injection of magnesium sulphate contained a very much greater amount of bile than the specimen of duodenal contents. Only one type of bile was, however, present. We were unable to confirm Lyon's claim that three distinct types of bile could be obtained. Dr. Haemerli, formerly assistant in Professor

Naegeli's Clinic in Zurich, tells us that he has seen the action of magnesium sulphate demonstrated during the performance of a laparotomy: a strong solution of the salt was injected into the duodenum and vigorous peristalsis of the gall-bladder was observed.

Although in many instances the cultural and microscopical characteristics of the duodenal and gall-bladder contents were identical, this is by no means constantly the case. For instance, in the gall-bladder group the duodenal contents contained leucocytes in fourteen instances, the gall-bladder contents in eighteen; cholesterol crystals were present on five duodenal contents, but in thirteen gall-bladder contents. These facts serve to show the value of the information obtained, especially in suspected gall-bladder cases, after injection of magnesium sulphate compared with the investigation of the duodenal contents alone.

It is an interesting fact that, although for investigation purposes it is best to inject the magnesium sulphate directly into the duodenum, it is possible to obtain a free flow of bile when magnesium sulphate is given by the mouth. This we have been able to prove experimentally. The duodenal tube was passed and allowed to enter the duodenum; magnesium sulphate was then given orally. No immediate result was obtained as in the direct method, but constant suction with a record syringe demonstrated an abundant flow of bile after a considerably longer interval, about fifteen to twenty minutes being the average time required. This fact has an important bearing on the treatment of gall-bladder infections, as by this means we have a valuable method of draining the biliary passages without resorting to cholecystostomy. The daily passage of a duodenal tube, as recommended by Lyon, for the non-surgical drainage of the gall-bladder, is also proved to be quite unnecessary.

Unfortunately most of the cases of gall-bladder disease were under observation only for a short period while a diagnosis was being established, and except in very few instances it was not possible to obtain second specimens in order to check the progress of treatment. In three cases only was this possible; in each of these the gall-bladder contents were examined again after urotropine had been administered in a single dose of from forty to eighty grains given at night. The second specimens in each case failed to give any growth of *B. coli*, which had previously been present, and the drug was detected in the bile obtained.

In addition to the administration of urotropine, a course of vaccine from the organism isolated from the gall-bladder contents was given, and a daily dose of magnesium sulphate

administered an hour before breakfast in order to promote drainage of the biliary tract.

Although the number of cases investigated after treatment is so few, the results obtained encourage us to believe that the duodenal tube can be of use not only in arriving at a diagnosis, but also as a means of obtaining the infecting organism, from which a vaccine can be prepared, in cases of gall-bladder disease and of Addison's anæmia, and as a control of progress. It would also seem that treatment given on the above lines is successful in removing biliary sepsis.

From the results obtained in this series of a hundred specimens it seems clear that, except in patients with achlorhydria, the presence of coliform bacilli in the gall-bladder bile should be regarded as evidence pointing to the probable presence of disease of the biliary tract. When in addition to coliform bacilli leucocytes are present, the evidence is more nearly conclusive. Finally, if cholesterol crystals are also found, we are almost justified in diagnosing gall-bladder disease.

Contrary to the finding of Rosenow, in our experience the infecting organism in cholecystitis is almost invariably *B. coli*, as in no case was it possible to demonstrate a streptococcal infection. In cases of achlorhydria infection with *B. coli* is not by itself so important, but when found in addition to the presence of leucocytes, and especially cholesterol crystals, the probability of gall-bladder disease must be carefully considered. If, however, a streptococcus, either with or without *B. coli*, is grown from the duodenal contents in a case of achlorhydria, a complete blood examination, including the plotting of a Price-Jones cell-distribution curve and van den Bergh's test, should be carried out, as even in the absence of any symptoms of the disease the case should be regarded as a potential one of Addison's anæmia.

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## A NOTE ON GALL-STONE FORMATION

By F. A. KNOTT, M.D., Pathologist to New Lodge Clinic and Clinical Assistant, Medico-Neurological Clinic, Guy's Hospital, and E. W. BOWELL, M.A., Assistant Clinical Pathologist, Guy's Hospital.

IN view of the uncertainty which still exists as to the sequence of events in gall-stone formation, it is hoped that this short series of cases may be of interest, because the stone-containing gall-bladders were obtained under specially favourable circumstances. In cases under their care Dr. A. F. Hurst and Mr. R. P. Rowlands kindly allowed us to examine the gall-bladders immediately after their surgical removal. We are also indebted to Dr. J. J. Conybeare for assistance in collecting case histories.

The results of these examinations are reviewed in relation to the two opposing theories of gall-stone formation: the infective, as originally upheld by Naunyn<sup>1</sup> and later supported by the work of Rosenow,<sup>2</sup> and the biochemical as suggested by the experiments on biliary precipitation by Chauffard<sup>3</sup> and Aschoff,<sup>4</sup> and more recently by the observations of Rovsing,<sup>5</sup> who found in 530 cases of gall-stones that the contents of the gall-bladder were sterile in 314, and who therefore expressed the opinion that infection was always secondary.

### ROUTINE OF EXAMINATION

The gall-bladders were immediately opened with strictly aseptic precautions and cultivations, aerobic and anaerobic, made from the bile, the external layers and centres of the stones, and portions of the bladder walls. The bile was examined microscopically for crystals, leucocytes, epithelial fragments, bacteria, etc. The stones were examined in section and their nature observed. Stained sections of the walls were prepared and examined histologically and for bacteria.

### GENERAL ANALYSIS

From so few cases it is impossible, of course, to draw absolutely definite conclusions, but we believe that our series includes instances of gall-stone formation, the mechanism of which can be explained only upon the assumption that neither the bacteriological nor the biochemical theory can possibly stand alone.



We consider that in most cases both factors must at one time or another come complementarily into play.

Illustrating the biochemical factor, it is seen that in six out of the eight cases in which the fresh, unopened gall-bladder was received, the fresh bile contained many small cholesterol crystals, and that in five of these the same crystals had, prior to the operation, been detected in the bile obtained by a duodenal tube. It seems fair to assume, therefore, that these free crystals were present in the gall-bladder before its surgical removal. The bile surrounding stones containing much pigment was in each case very dark and viscid; that in contact with the cholesterol stones was very much lighter. In each case the bile was evidently in an easily precipitable condition, so that whatever focus for crystallisation might present itself, stone formation would readily occur. We could not confirm Rovsing's view that each stone has a centre composed essentially of bile pigment.

Bacteriologically it is noteworthy that in eight of the ten cases there was complete sterility of the bladder and contents irrespective of the type of stone. Except in the two actively infected cases (Nos. 4 and 10), no existing deposition or liberation of leucocytes could be found. As described later, the histological appearances of the walls suggested that all active bacterial invasion had ceased long ago. An instance of an active inflammatory stage is seen in Case No. 10, while Case No. 4 is evidently an instance of a late secondary infection following the initial cholecystostomy. In contrast with Rose-now's findings, we could find in the walls no evidence of the persistence of streptococci.

#### EFFECT OF EPITHELIAL DESQUAMATION

The appearance of the walls of these sterile bladders makes it probable that in the past active bacterial infection was present, and our reading of the sections made is that in each case there has been an inflammatory event, of which gall-stone formation is a late and indirect result. In each we have found more or less mutilation of the epithelium and frequently almost complete desquamation. Allowing that this may partly be a post-mortem phenomenon, it is sufficiently clear, owing to the freshness of our specimens, that the condition exists in the living body when gall-stones are formed. When ordinary epithelium is damaged, a process of repair very soon comes into evidence. But, in the presence of bile, it must be singularly difficult for the gall-bladder epithelium to repair itself. After

## CASE SERIES.

Gall-bladder removed at operation.

No.	Case.	Clinical Notes.	Gall-bladder Bile.	Stones.	Histology of Gall-bladder Wall.			
					Thickness.	Bile Staining.	Epithelium.	Inflammation.
1	R. M. G. male, at. 57.	Attacks of rt. epigastric pain and flatulence for many years. First typical gall-stone colic in 1921, second in 1922. No previous disease. Never had typhoid. Cholecystectomy Nov. 1922. Gall-bladder bile before operation, obtained via duodenal tube, contained cholesterol crystals but no leucocytes. Cultivations practically sterile.	Clear, light-coloured bile containing no leucocytes. A small number of cholesterol crystals present. No bacteria seen. Cultures all sterile.	30 small stones of almost pure cholesterol. All cultures sterile.	Very thin.	Inner half stained.	Almost absent.	Long extinct.
2	A. B. female, at. 57.	Dyspeptic symptoms for previous ten years. Eight pregnancies. First attack of typical gall-stone colic early in 1922. Numerous attacks since. Gall-bladder bile via duodenal tube contained many small cholesterol crystals but no leucocytes. Cholecystectomy in Nov. 1922.	Clear, light-coloured bile containing no leucocytes but showing many small cholesterol crystals. No bacteria seen. Cultures all sterile.	180 faceted stones composed mainly of cholesterol, some with central pigment. All cultures sterile.	Twice normal thickness.	Below damaged epithelium.	Damaged and partially necrotic (see Fig. 2).	Chronic type.
3	B. de L. female, at. 38.	Mild dyspeptic symptoms for many years. Typical gall-stone colic first experienced in 1922, several attacks since with pain and jaundice. Three pregnancies. Bile obtained by duodenal tube before operation contained a few leucocytes and many small cholesterol crystals.	Clear, yellowish bile containing no leucocytes but cholesterol crystals present. No bacteria seen. Cultures all sterile.	18 medium-sized stones containing about 60% cholesterol. All cultures sterile.	Three times normal thickness.	Inner necrotic layer stained.	Chiefly persisting in cavities (see Fig. 4).	Chronic with more fibrosis than Case 2.
4	S. L. female, at. 38.	After dyspeptic symptoms over many years and several typical attacks of colic, cholecystectomy performed in 1922 and several stones removed. Failure in wound closure caused second operation six months later: gall-bladder removed. Three small stones removed from common duct. Bile via duodenal tube contained many leucocytes and <i>B. coli</i> .	Clear, non-viscid bile containing a number of leucocytes but no cholesterol crystals. Cultures gave a strong growth of <i>B. coli</i> .	3 small stones composed mainly of cholesterol and lying in the common duct. All cultures gave a strong growth of <i>B. coli</i> .	Considerable thickening, fibrosis and oedema.	At damaged areas only.	Disordered; only partial desquamation.	Subacute.
								Many <i>B. coli</i> grown from the bladder walls.

5	Mrs. E. et. circ. 50.	Long history of dyspepsia and more recently attacks of gall-stone colic. No specimen via duodenal tube obtained.	Very dark, viscid bile containing neither leucocytes nor crystals. All cultures sterile.	2 large, soft, dark-coloured stones containing a high percentage of pigment. All cultures sterile.	Thin: little but fibrous tissue and vesiculae.	Stained through whole thickness.	Occasional fragments remain (see Fig. 5).	Long extinct.	No bacteria found in the wall. All cultures sterile.
6	E. T. male, et. 47.	Indigestion for three years and one year of attacks of biliary colic. Operation: cholecystectomy; also chronically inflamed appendix removed and a small duodenal ulcer invaginated.	Clear, light-coloured bile containing small cholesterol crystals but no leucocytes. All cultures sterile.	7 small stones of almost pure cholesterol. All cultures sterile.	Thicker, but otherwise as Case 5.	Stained through whole thickness.	Fragments only remain.	Long extinct.	No bacteria seen in wall. All cultures sterile.
7	Miss R. et. 64.	Repeated attacks of epigastric pain and biliary colic over two years. Operation: nothing abnormal in abdomen except cholelithiasis. Cholecystectomy performed.	Dark-coloured bile containing many cholesterol crystals but no leucocytes. Cultures for pathogenic organism all sterile.	56 large and small stones consisting mainly of cholesterol but with about 30% of pigment.	Increased considerably.	Inner half stained.	Fragments only remain.	Not recent.	No bacteria found in the walls.
8	E. M. female, et. 68.	Dyspeptic symptoms for many years, and for two years several attacks of typical gall-stone colic. Had typhoid at age of seventeen years. Operation at close of an attack of colic: cholecystectomy.	Dark, viscid bile in which no bacteria, leucocytes or cholesterol crystals could be seen microscopically. Cultures not made.	One large stone consisting of about 50% pigment and 50% cholesterol. No bacteria detected in films. No cultures.	Great hypertrophy: new fibrous tissue.	Occasional staining.	Irregular with many "glands" (see Fig. 8).	Chronic type.	No bacteria seen in the sections.
9	M. W. female, et. circ. 45.	Long history of epigastric pain and dyspepsia with several recent attacks of biliary colic. A sample of duodenal contents removed by puncture at operation contained neither leucocytes nor crystals.	Very dark, viscid bile containing very occasional leucocytes and epithelial cells but no crystals. Cultures all sterile.	A single large stone consisting almost entirely of bile pigment. All cultures sterile.	Increased: vascular hypertrophy.	At margin of epithelium chiefly.	Damaged: large portion of epithelium remaining intact.	Chronic type: round cell infiltration.	All cultures sterile.
10	K. C. female, et. 50.	Repeated attacks of epigastric pain for a number of years, with recent attacks of biliary colic. The bile via duodenal tube contained a number of leucocytes and a few small cholesterol crystals. Cultivations gave a strong growth of <i>B. coli anaerogenes</i> .	Very dark, viscid bile containing leucocytes, small cholesterol crystals and many bacilli. Cultures: strong <i>B. coli anaerogenes</i> .	One large soft stone containing about 60% pigment, 40% cholesterol. Cultures: strong growth of <i>B. coli anaerogenes</i> .	Increased: hyperemic, lymphatic adenoma.	Occasional in epithelium only.	Edematous: occasionally stripped (see Fig. 1).	Active sub-acute type.	Numerous bacteria are seen among the remains of the mucosa. Cultures: a pure growth of <i>B. coli anaerogenes</i> .

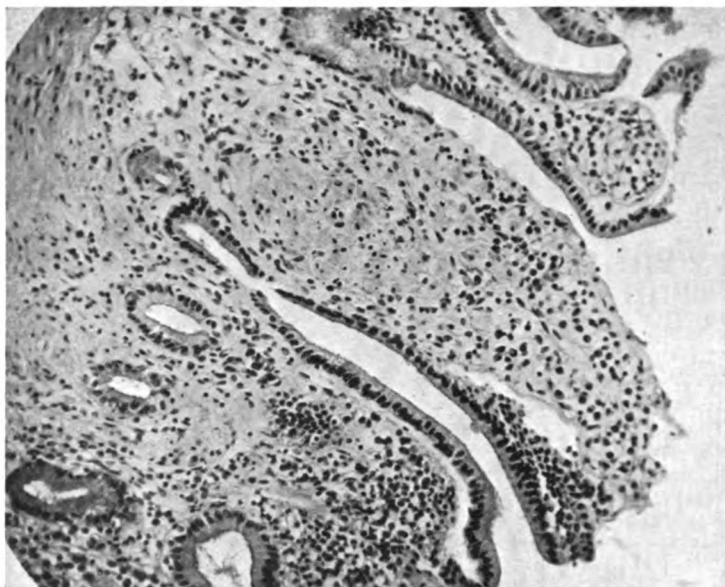


FIG. 1.

Active cholecystitis: œdema, leucocytes; partial stripping of the epithelium.  $\times 150$ .

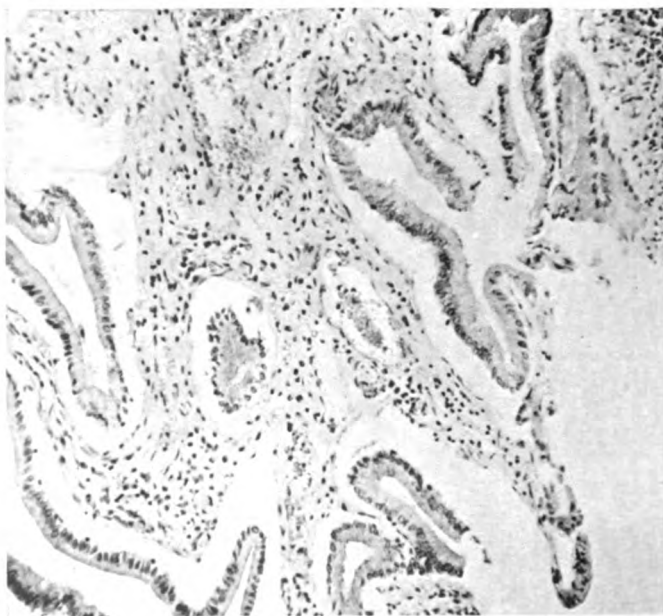


FIG. 2.

Active inflammation has ceased: but the results of the œdema are still seen.  $\times 150$ .

examining a large number of sections we have been unable to discover an instance in which it has been satisfactorily achieved. We have seen the conversion of masses of columnar epithelium into a more or less good imitation of squamous epithelium (*vide* Nicholson <sup>6</sup>), and in one case in which this has happened the results are obviously ineffective so far as protection of the wall is concerned: the whole tissue is œdematous and deeply bile-stained. Repair of the gall-bladder epithelium after any considerable inflammatory desquamation must be an unusual occurrence, and this failure must inevitably result in marked penetration of the wall by bile, which, owing to its low surface tension, possesses a power of permeating tissues equalled by few other fluids. In short, the mucus-forming epithelium is evidently the sole effective barrier between the fluid bile and the gall-bladder wall.

#### PROTECTIVE FUNCTION OF THE GALL-BLADDER EPITHELIUM

The fate of this epithelial lining, after it is once broken through, is well illustrated in our cases. Normally the mucus-forming cells are very similar to those which line the cervical endometrium; they also resemble the cells of the mucus glands of the respiratory passages. The cytoplasm is regular and uniform in appearance, and there is a distinct bar of clear mucus across the free ends of the cells external to the cytoplasm. If the epithelium is normal, the cells will be obviously living and there will be no staining of their cytoplasm by bile, which is seen not to pass through when this mucus bar is intact.

We think that the importance to the hollow viscera of this protective function of mucus cannot be too strongly emphasised. If it were not for this material, practically none of the chemistry of the body could be carried out in the structures actually used. Mucus forms, in fact, the walls of the living test-tube. It serves also a most important purpose in restraining bacterial action. While the organisms are surrounded by mucus they are, so to speak, insulated. Mechanically also the material is obviously of the highest importance.

#### RESULTS OF LOSS OF THIS EPITHELIUM

Having described the natural defence against bile possessed by the gall-bladder walls, we may call attention to the effects of its breakdown. Fig. 1 represents active inflammation (Case 10), where there is an accumulation of leucocytes, general œdema, and some superficial loss of epithelium resulting from the œdema. Most of the cells present are, however, still living. Fig. 2 shows



FIG. 3.

Active inflammation has ceased: there is extensive bile-staining of the epithelium and the wall.  $\times 150$ .

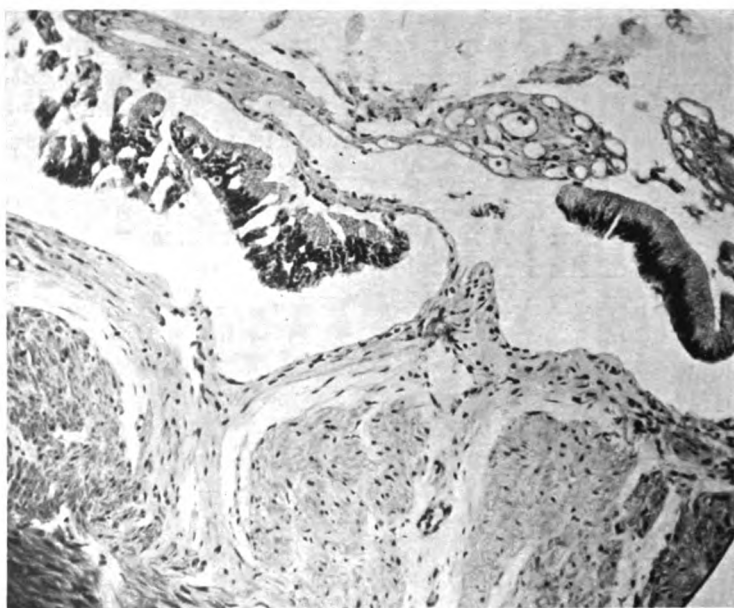


FIG. 4.

Bile-staining of the wall: relics of bile-stained and partially necrotic epithelium in the cedematous spaces.  $\times 150$ .

the condition after the subsidence of acute inflammation. Figs. 3, 4, and 5 show later stages. The bile first stains the damaged epithelium and then enters the muscular layers beneath. The wall is in the normal state extremely thin. It consists of two delicate networks of muscular strands and rarely presents any appearance of solidity. In the interspaces there are vessels and nerves and a minimal amount of connective tissue. But when the epithelium is damaged, even apparently by a simple inflammation, there is a pronounced thickening of the wall. This thickening is in the present cases of the nature of fibrosis, and evidently represents an attempt to compensate for the loss of the barrier of epithelium. The fibrosis is, however, of a weak type: its formation has been checked by the presence of the bile in the deeper layers of the wall, so that there is a great tendency for strips of the more necrotic innermost layer to become loosened. We suggest that this is the usual method by which a concretion once formed in the wall becomes free.

#### GALL-STONE FORMATION

With regard to actual stone formation, we have been fortunate in finding several instances of the earliest stages of this process. A typical instance is illustrated in Figs. 6 and 7. Chauffard <sup>7</sup> suggests that the method of intramural stone formation is in the first place a deposition of desquamated epithelium, pigment and cholesterol at the bottom of Luschka's canals, which ultimately close over the deposit, allowing it to develop into a minute stone. Gosset, Loevy and Magron <sup>8</sup> have described another method: the appearance of cholesterol spherules apparently forming in the subepithelial tissue of the wall and being ultimately extruded from the mucous membrane of the gall-bladder. In both cases further deposition of biliary constituents upon the original small concretion is held to occur. If, however, we remember the power of penetrating the wall possessed by the bile, it seems probable that these two supposedly different methods of stone formation are in reality manifestations of one and the same process, namely, saturation of the tissues by bile.

The muscular coat of the bladder, especially its inner layer, is a loose network and there is little submucous connective tissue; the weakened epithelium is thus always inclined to dip inwards and line a series of little pits. If the muscular wall contracts more violently than usual, as it may in the presence of an inflammatory or irritating agent, the epithelium of the

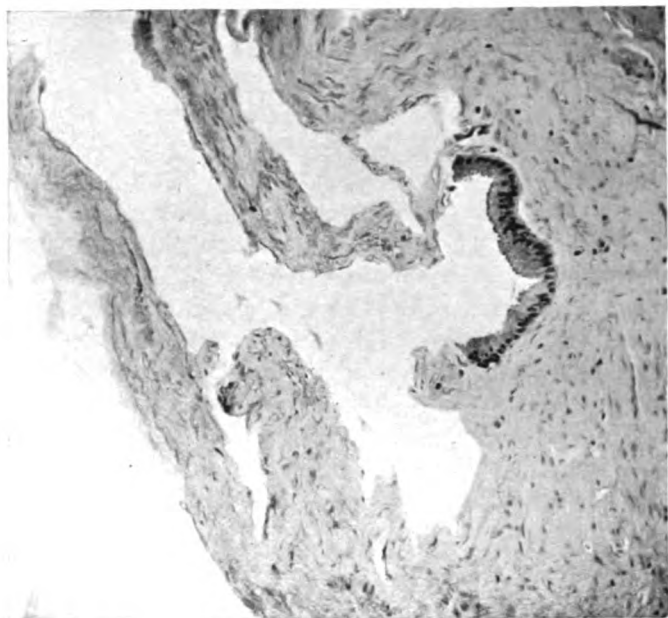


FIG. 5.

Fragment of persisting epithelium with bile-staining of its free edge.  $\times 150$ .

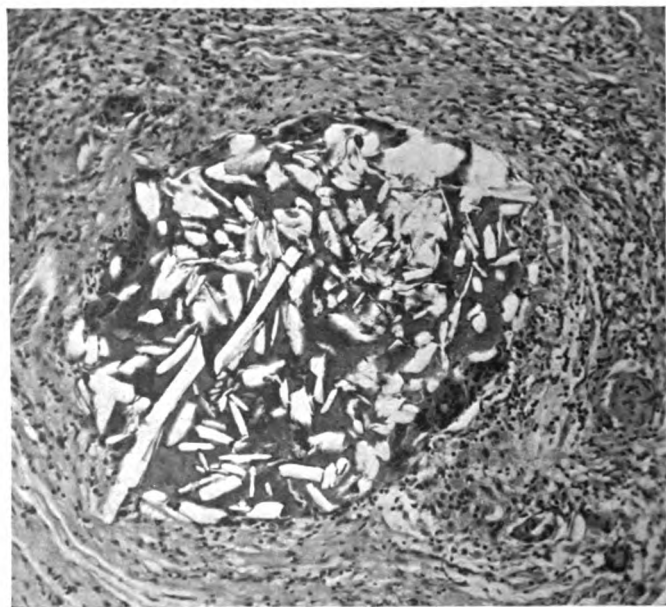


FIG. 6.

Gall-stone; early stage; pigment and crystals with giant cells.  $\times 75$ .



pits will be caught up and imprisoned in the wall so as to form, in section, structures like irregular glands (Fig. 8).

Where the epithelium is already bile-saturated and a relatively large piece has thus been sequestered, we probably have the earliest phase in the formation of the larger type of intramural gall-stone. A small amount of actual bile has been imprisoned in the wall, the cavity being lined with damaged epithelium and forming a sequestration cyst. In our illustration (Fig. 6) the bile is represented by pigment and crystals. The epithelium retains its original form in a small part only of the lining; elsewhere it has apparently been converted into multinuclear giant cells which are seen to possess the same staining characteristics as the epithelial cells.\* Their nuclei stain deeply, their cytoplasm also stains a light bluish colour with hæmatoxylin. This feature may probably be taken as indicating the presence of more calcium than usual in the cytoplasm, and we suggest that some at least of the calcium found in gall-stones arises directly from the action of these giant cells. Admittedly the ordinary process of calcification of foreign bodies is associated with the presence of similar cells.

If, on the other hand, only a small portion of bile-saturated epithelium (cf. Fig. 4) is held in the originally submucous tissue, then, as the cells become necrotic, it will leave a very small nucleus of biliary constituents in the wall. After solidification these superficial deposits will be relatively quickly extruded through the remaining epithelial layer and so produce the cholesterol spherules described by Gosset, Loevy and Magron. That both these and the more deeply intramural deposits can be precursors of gall-stones does not seem open to doubt. But we suggest that the mechanism of production of both types of original concretion is the same; namely, damage to the mucous layer, and that only the amount of the imprisoned bile and the depth of its penetration into the wall are variables.

#### CHOLECYSTITIS AND BILIARY CONCENTRATION

It is possible that the original epithelial damage might be produced by concretions arising from spontaneous crystallisation from sterile but concentrated bile. But it seems more likely that a temporary bacterial cholecystitis would be a frequent, if not the usual starting-point. The poor chance of repair possessed by the damaged mucous lining has already been illustrated. It would, presumably, be quite unnecessary for the ultimate development of gall-stones that an infection

\* It is, of course, possible that these giant cells may be really metamorphosed leucocytes and not epithelial in origin.

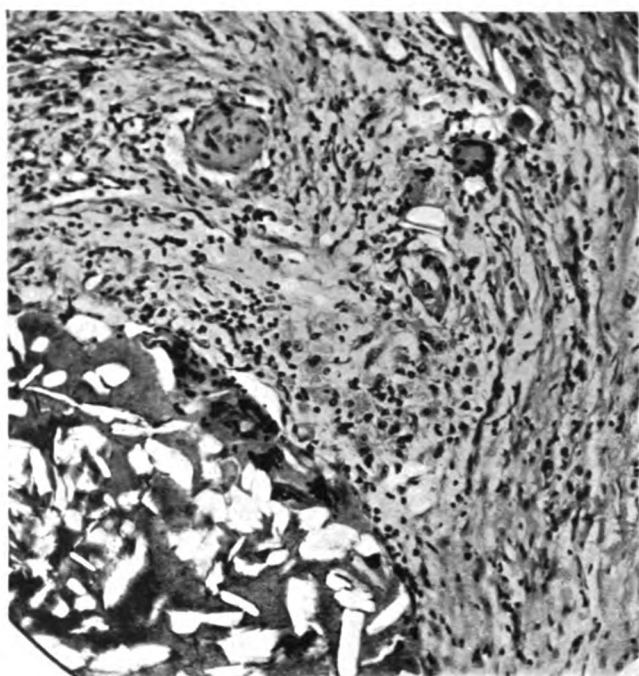


FIG. 7.

Enlarged from a part of fig. 6, showing detail of giant cells, and resemblance to tuberculous granulation tissue.  $\times 150$ .

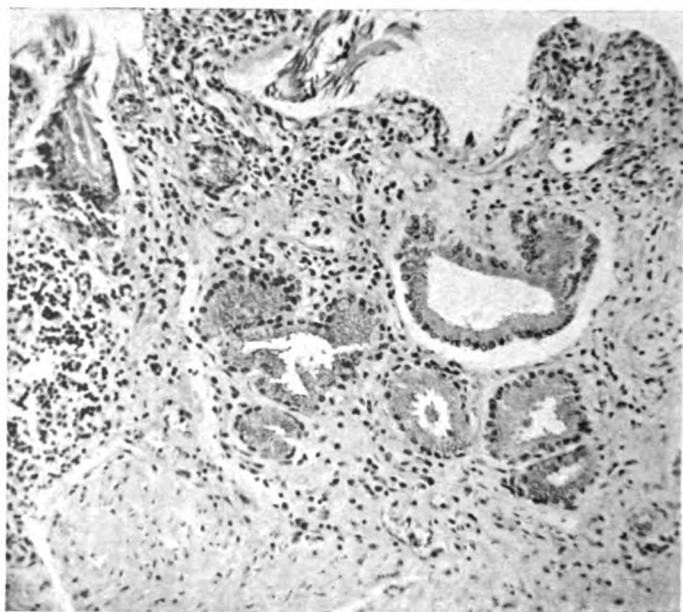


FIG. 8.

Chronic inflammatory condition. The imprisoned epithelium forms rosettes: but the condition of the cells shows that these structures are abnormal.  $\times 150$ .

should persist once extensive desquamation and biliary penetration of the wall had begun.

Microscopical intramural concretions are frequently found in large numbers in old cases of cholecystitis which show no macroscopic stones. There is no reason to doubt that these tiny concretions could be the precursors of large stones, but, on the other hand, cholecystitis is admittedly not always followed by true gall-stone formation, and therefore it seems more than probable that concentration and stagnation of the bile are also necessary before typical gall-stones develop.

#### CONCLUSIONS

It is difficult to explain the condition found in the eight sterile gall-bladders except on the assumption that a bacterial cholecystitis had previously occurred. We suggest that, although this infection had died out, its effects upon the mucous lining of the bladder resulted in the production of microscopic stones by the method described.

Once epithelial desquamation has occurred, the process of stone formation would appear to be independent of the persistence of the infection, for in Case No. 10 there is an active cholecystitis combined with other appearances closely resembling those of the sterile cases.

So far as we can see there is no necessity for the presence of any foreign body, other than the necrotic bile-saturated epithelium, as a nucleus for the original microscopic gall-stones; that bacteria should sometimes be included or enter these structures is natural enough: it would be remarkable if they did not.

An essential factor in gall-stone formation may well be the power possessed by the bile, once the lining epithelium is damaged, of penetrating the gall-bladder wall.

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# GALL-STONES:

## AN ACCOUNT OF ONE HUNDRED AND SEVENTEEN CASES \*

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### INTRODUCTION

It is proposed to give an account of an investigation of one hundred and seventeen cases of gall-stones, in which there is a record of the symptoms and signs before operation, of the conditions found at operation and the operative treatment, and of the after-history for six to twenty-one years. The cases formed a consecutive series in the surgical wards of Guy's Hospital.

### THE INCIDENCE OF GALL-STONES

In this series ninety-four (80.5 per cent.) were in women and twenty-three (19.5 per cent.) were in men.

Of the ninety-four women, eighty-four (88 per cent.) were parous, the number of pregnancies in each case varying from one to sixteen. In the case of young women the onset of symptoms of gall-stones definitely followed the first pregnancy.

With regard to previous diseases, twelve had had scarlet fever or measles, four lobar pneumonia, three typhoid fever, three catarrhal jaundice in childhood, three pleurisy, three diphtheria, two appendicitis, two acute rheumatism, one erysipelas (two months before the onset of acute symptoms of gall-stones), one strangulated femoral hernia, one dysentery, one "remittent fever," one small-pox, and one a pancreatic cyst. In ten there was no history of pregnancy; and in four no history of previous disease.

Of the twenty-three men, there was no history of previous disease in thirteen (56 per cent.). Three had had scarlet fever, one measles, one appendicitis, one hepatic abscess (drained fifteen years before the operation for gall-stones), one rheumatic fever, one *Bacillus coli* pyelitis, one gonorrhœa, and one enteritis from food poisoning.

\* Part of the expense of this research was defrayed by a grant from the Clinical Research Committee, Guy's Hospital.

The rarity of symptoms of gall-bladder disease following acute portal or systemic infections is very striking.

#### THE SYMPTOMS AND SIGNS OF GALL-STONES

In this series the symptoms were as follows :—

Flatulence and indigestion (distension after meals) . . . . .	100 cases (85%).
Pain . . . . .	98 „ (84%).
Vomiting . . . . .	59 „ (50%).
History of an attack or attacks of jaundice . . . . .	50 „ (48%).

The early symptoms are flatulence and fullness after meals with nausea. In many these are the only symptoms noted. The flatulence and distension are more remarkable for their persistence than their intensity.

In the majority the pain is not severe and is referred indefinitely to the epigastrium. If the pain is severe, it shows that the stone or stones are producing mechanical effects by obstruction, or that inflammation has spread to the serous coat of the gall-bladder or to the parietal peritoneum. In thirty cases (26 per cent.) the pain was typical of gall-stone colic, and was sudden and agonising, commencing in the epigastrium, passing across the abdomen into the right and in two cases into the left shoulder. Shoulder pain is not typical of gall-stone colic—it is more marked in cases of perforated duodenal ulcer, where there is extreme spasm of the diaphragm. The shoulder pain is due to irritation of sensory fibres of the phrenic nerve. Stabbing pain in the right hypochondrium is a common result of impaction of a stone in the neck of the gall-bladder or cystic duct. Vomiting was present in cases of stone in the neck of the gall-bladder, cystic duct and common bile duct, and in acute gall-stone colic.

A history of jaundice is not a reliable symptom of gall-stones unless accompanied by a typical history of colic. In all cases the jaundice is the result of the presence of gall-stones, and is due to a catarrhal infection of the ducts with or without obstruction of the common bile duct by a stone.

In this series the signs were as follows :—

Tumour (in one case the kidney explored first and found normal) . . . . .	43 cases (36%).
Tenderness over gall-bladder . . . . .	46 „ (39%).
Tenderness in right iliac fossa (appendix not inflamed) . . . . .	7 „ (6%).

Jaundice . . . . .	18 cases (15%).
Rigidity . . . . .	10 „ (8.5%).
Bile in urine . . . . .	8 „ ( 7%).
Sugar in urine (case of chronic pancreatitis with gall-stones) . . . . .	1 case (0.8%).
Clay-coloured fæces . . . . .	6 cases ( 5%).
Liver enlarged (in both cases jaundice was present) . . . . .	2 „ (1.7%).
Spleen enlarged (cirrhosis of the liver, with ascites and gall-stones) . . . . .	1 case. (0.8%)

Where a tumour was felt the gall-bladder was enlarged, its walls were thickened, or the subject was thin.

Jaundice was present in fifteen per cent. of the cases. In eight it was definitely obstructive in character and associated with bile in the urine. In six of these the fæces were clay-coloured. The dangers of operating in the presence of deep jaundice will be dealt with on another occasion.

#### THE DURATION OF SYMPTOMS BEFORE OPERATION

In this series the duration of symptoms before operation was as follows :—

	Number of Cases.	Per- centage.
One year or less . . . . .	46	39
Two years . . . . .	30	25
Three years . . . . .	5	4
Four years . . . . .	7	6
Five years . . . . .	1	0.8
Six years . . . . .	5	4
Seven years . . . . .	3	2.5
Eight years . . . . .	3	2.5
Ten years . . . . .	5	4
Twelve years . . . . .	2	1.7
Fourteen years . . . . .	1	0.8
Fifteen years . . . . .	1	0.8
Seventeen years . . . . .	2	1.7
Twenty years . . . . .	3	2.5
Twenty-six years . . . . .	1	0.8
Thirty years . . . . .	1	0.8

These figures give no information as to how long the gall-stones have been in the gall bladder. It is known that gall-stones may be present for many years without giving rise to symptoms, being discovered during operations for other conditions or at

post-mortem examinations. However, they do show that once symptoms or complications had arisen, 39 per cent. sought surgical relief within one year, 64 per cent. in two years, 74 per cent. in four years, 10 per cent. in periods varying from five to ten years, 7½ per cent. in periods varying from eleven to twenty years, and 1·5 per cent. in from twenty-one to thirty years.

AGE AT WHICH OPERATION WAS PERFORMED

Age.	Women.		Men.	
	Number.	Percentage.	Number.	Percentage.
20-29	3	3	2	9
30-39	26	28	0	0
40-49	23	24	13	56
50-59	33	35	6	26
60-70	9	9	2	9

The figures show that fifty-five per cent. of the women were operated upon during the normal child-bearing period. Forty-four per cent. of the women were operated upon between the ages of fifty and seventy—the period of adiposity, diminution of thyroid secretion, fibroid and fatty changes in the heart, and degeneration of the blood vessels. Ninety-one per cent. of the men were operated upon between the ages of forty and seventy—the period when degenerative changes in the blood-vessels occur, which may be associated with hypercholecystolæmia.

#### OPERATIVE TREATMENT

1. *Cholecystostomy*.—The gall-bladder was drained in seventy-six cases, and in seven of these choledochotomy was also performed.

The gall-stones were distributed in the biliary apparatus as follows :—

Stones (varying in number from one to three hundred and twenty-nine) in the gall-bladder only . . . . .	54 cases.
Stones in the gall-bladder and cystic duct . . . . .	7 „
Stones in the gall-bladder and common bile duct . . . . .	8 „
Stones in the cystic duct only . . . . .	6 „
Stones in the common bile duct only . . . . .	1 case

In seven instances the stones were removed from the common bile duct by incision with choledochotomy.

In one instance two stones were pushed from the common bile duct into the duodenum by manipulation.

In one instance two stones were milked from the common bile duct through the cystic duct into the gall-bladder.

In sixty-five cases the biliary apparatus was approached through a vertical incision. In two of these a transverse incision was made at a later stage to get an adequate exposure. In eleven the oblique, Kocher's or Bevan's, incision was made.

The difficulties met with during the operations will be discussed on another occasion.

*The results of cholecystostomy.*—(a) *Immediate.*—On the average the cases of cholecystostomy were twice as long in hospital as the cases of cholecystectomy.

There were five cases of biliary fistula, four of suppuration in the wound (in one of these the wound was resutured under an anæsthetic), one of abscess in the right kidney pouch requiring drainage, one of *Bacillus coli* cystitis, and one of femoral thrombosis.

(b) *Remote.*—In seven cases (9 per cent.) there was a recurrence of gall-stones, producing symptoms requiring further operation. In all of them stones were found in the gall-bladder only at the first operation. In one the common bile duct was drained. The details of these seven cases are as follows :—

1. Twenty years later, gall-stones in the gall-bladder; cholecystostomy. Still has flatulence and indigestion.

2. Twenty-one years later, gall-stones in the gall-bladder; cholecystostomy. Still has flatulence and indigestion.

3. Seven years later, gall-stones in the gall-bladder; cholecystostomy and choledochotomy. Still has attacks of flatulence, indigestion, abdominal pain and of jaundice.

4. Six months later, cholecysto-duodenal fistula; four stones removed from gall-bladder and one from common bile duct; cholecystostomy and choledochotomy. Patient died five years after second operation at the age of sixty-three. Flatulence and indigestion persisted until death.

5. Five years later, four stones removed from the gall-bladder; cholecystostomy. Still has flatulence, indigestion and abdominal pain.

6. Eight years later, stone removed from gall-bladder; cholecystostomy. Still has indigestion and abdominal pain. There is a ventral scar hernia.

7. Nine months later, the gall-bladder was removed and four stones were found in it after removal. Has been perfectly well since.

In one case (not included as a recurrence of gall-stones)



death took place four months after the first operation. The post-mortem showed that death was due to obstruction of the ileum by an impacted gall-stone.

In the seventy-six cases there were nine incisional hernias; eight (12 per cent.) were through vertical scars and one (9 per cent.) through an oblique incision which was followed by suppuration.

In twenty-two (30 per cent.) there is complete relief from symptoms, but three of these have an incisional hernia.

Of the remaining cases, six complain of flatulence, indigestion, abdominal pain and have had attacks of jaundice; seven complain of indigestion and abdominal pain; three complain of flatulence and indigestion and have had attacks of jaundice.

Thirty (39 per cent.), although not completely cured, are much relieved.

To sum up: 30 per cent. are cured, 39 per cent. are very much better, 13 per cent. are partially relieved and 8 per cent. are unrelieved. Nine per cent. required further operation for recurrence of gall-stones.

2. *Cholecystectomy*.—The gall-bladder was removed in thirty-six cases and in four of these choledochotomy was also performed.

The gall-stones were distributed in the biliary apparatus as follows:—

Stones (varying in number from one to eighty) in the gall-bladder only . . .	26 cases
Stones in the gall-bladder and cystic duct . . .	4 „
Stones in the gall-bladder and common bile duct . . . . .	4 „
Stones in the cystic duct only . . . . .	2 „

In one instance the kidney was explored first and found normal, in one the appendix was explored through a gridiron incision and found normal. In two, acute appendicitis was associated with gangrene of the gall-bladder and gall-stones. One case was a cholecystectomy for recurrence of stones in the cystic duct following cholecystostomy.

Of the four cases of choledochotomy in addition to cholecystectomy, the common bile duct was drained through the stump of the cystic duct in one and through an incision in the common bile duct in three.

In thirty-one cases the biliary apparatus was approached through a vertical incision. In five the oblique Kocher's or Bevan's incision was made.

*The results of cholecystectomy*.—(a) *Immediate*.—On the

average the case of cholecystectomy were half as long in hospital as the cases of cholecystostomy.

There were no cases of biliary fistula; one had suppuration in the wound and one had a sinus in the right loin following a negative exploration of the kidney.

(b) *Remote*.—There are no signs and symptoms pointing to recurrence of stones, and no further operations have been performed on the biliary apparatus. One was operated on eleven years later for gastric ulcer.

In twenty (55·5 per cent.) there is complete relief from symptoms, but two have an incisional hernia. In five of these the oblique incision was made, and there are no ventral hernias. In the thirty-one instances in which a vertical incision was used there are two incisional hernias (6 per cent.).

Of the remaining cases, one complains of flatulence, indigestion, abdominal pain and has had attacks of jaundice (the gall-bladder was opened accidentally at the operation), two have slight flatulence and occasional pain in the abdomen (in one of these a gastric ulcer was excised eleven years after the cholecystectomy).

Thirteen (36 per cent.), although not completely cured are greatly relieved.

To sum up : 55 per cent. are cured, 36 per cent. are very much better, 5 per cent. are partially relieved and 3 per cent. are unrelieved. No case has required further operation for recurrence of gall-stones.

TABLE A  
RESULTS OF OPERATION

Operation.	Number of cases.	Cured.	Much better.	Partially relieved.	Unrelieved.	Incisional hernia.	Second operation.
Cholecystostomy . .	76	30%	39%	13%	7·9%	10%	9%
Cholecystectomy . .	36	55%	36%	5%	3%	5%	Nil

In five cases the results of operation are not included. In two, the gall-bladder was not opened, but the symptoms persisted. In three, the gall-bladder was opened, the stones were removed and the gall-bladder sutured (cholecystendysis). All three developed a biliary fistula in from three to six days after operation.

An analysis to compare the results of cholecystostomy with cholecystectomy, with or without choledochotomy, and the influence of a vertical or oblique incision is as follows :—

TABLE B

Treatment.		Number of cases.	Cured.	Second operation.	Result : Much better, partially relieved or unrelieved.				
Operation.	Incision.				Flatulence.	Indigestion.	Abdominal pain.	Jaundice.	Hernia.
Cholecystostomy. Cholecystostomy.	Vertical	60	14 (23%)	6 (10%)	33 (55%)	37 (61%)	20 (30%)	13 (22%)	7 (12%)
	Oblique	9	5 (56%)	0	1 (11%)	1 (11%)	1 (11%)	0	0
Cholecystostomy with choledochotomy. Cholecystostomy with choledochotomy.	Vertical	5	1 (20%)	1 (20%)	1 (20%)	1 (20%)	1 (20%)	1 (20%)	1 (20%)
	Oblique	2	2 (100%)	0	0	0	0	0	1 (50%)
Cholecystectomy. Cholecystectomy.	Vertical	28	12 (43%)	0	11 (39%)	11 (39%)	6 (21%)	2 (7%)	2 (7%)
	Oblique	4	4 (100%)	0	0	0	0	0	0
Cholecystectomy with choledochotomy. Cholecystectomy with choledochotomy.	Vertical	3	3 (100%)	0	0	0	0	0	0
	Oblique	1	1 (100%)	0	0	0	0	0	0

This analysis shows that :—

(1) The results of cholecystectomy are better than cholecystostomy.

(2) The results of cholecystectomy with choledochotomy are better than cholecystostomy with choledochotomy.

(3) The late results are better where choledochotomy was performed in addition to cholecystostomy or cholecystectomy.

(4) The results following the use of an oblique Kocher's or Bevan's incision are so much better than those following the vertical incision that, next to cholecystectomy, this appears to be the most important factor to ensure success.

(5) The symptoms which may persist after operation are indigestion, flatulence and abdominal pain. It is worthy of note that these symptoms were frequent only in the cases where cholecystostomy was performed or a vertical incision was made. The indigestion and flatulence with stasis in the stomach and intestine are the result of adhesions and of the presence of a gall-bladder with diseased walls and of an active or latent focus of infection within or around it.

The jaundice following operation is catarrhal in character and due to inflammation of the common bile duct from the

presence of a gall-bladder with diseased walls and of a focus of infection within or around it. In the two cases in which jaundice followed cholecystectomy the gall-bladder was opened accidentally at the operation. Jaundice following operation is prevented by cholecystectomy with choledochotomy.

Hernia following operation is the result of sepsis or of the use of a vertical incision.

When not associated with hernia or jaundice, the abdominal pain is located in the scar (latent infection) or is due to the factors which cause indigestion and flatulence. The absence of abdominal pain is remarkable in the cases where an oblique incision was used.

### CONCLUSION

The advantages of cholecystectomy are even more striking when the patients themselves are seen. It is proposed, therefore, to consider briefly some aspects of this operation. The operation is made more difficult by the adhesions which are so commonly present, but it must be remembered that even in cholecystostomy adhesions must be divided to explore thoroughly the biliary apparatus. If the disease is limited to the gall-bladder, as in empyema, there is less risk in removal than in drainage.

Recurrence of stones following cholecystectomy is very rare, and in some of the cases recorded it would appear that the stones were left at the first operation and were not of new formation. If the gall-bladder is removed, there is no risk of a biliary or mucous fistula, mucocele, empyema or carcinoma of the gall-bladder. The septic sequelæ of the operation itself and duodenal or gastric adhesions are less common after cholecystectomy.

When the gall-bladder is removed there follows a marked dilatation of the extrahepatic ducts, but the intra-hepatic ducts do not expand. The dilatation continues either until the extra-hepatic ducts contain as much bile as the gall-bladder or until the sphincter dilates. Cholecystectomy leads to dilatation of the sphincter so that the drainage of bile is more free. There is less risk of pancreatitis because of this more free drainage and because the focus of infection is removed.

Another important question is whether secondary operations on the common bile duct are more difficult when the gall-bladder has been removed. Secondary operations for stone in the common bile duct following cholecystectomy are less difficult because there are no adhesions due to the presence of the gall-

bladder and because the stone or stones themselves are a good guide as to the position of the common bile duct.

Cholecystectomy should, of course, not be performed when the jaundice is found to be due to causes other than stone, such as carcinoma of the pancreas, common bile duct or duodenum.

There are two conditions due to gall-stones in which primary cholecystectomy may be contraindicated—septic cholangitis with cholæmia and in acute cases where the extensive division of adhesions increases the immediate danger of operation.

The immediate risks and dangers of operations will be dealt with on another occasion.

## THE DIAGNOSIS OF GASTRIC AND DUODENAL ULCER WITH THE X-RAYS

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital, and  
P. J. BRIGGS, Radiologist to New Lodge Clinic.

THE x-rays stand supreme as a means of diagnosis of gastric and duodenal ulcers and their complications. Recent advances in technique have made it possible to recognise the presence of chronic ulcers, whether small or large, recent or of long standing, with almost complete certainty in a very large percentage of cases. The x-rays give further valuable information as to the nature and extent of the disturbances in the motor functions of the stomach, which result from the presence of an ulcer, and in this way useful indications for treatment are obtained. Lastly, they afford an indispensable guide as to the effect of treatment, as no case of chronic ulcer should be regarded as cured until the apparent recovery is confirmed by the disappearance of the radiographic signs to which it originally gave rise, with the exception of those resulting from permanent deformities caused by the cicatricial contraction of fibrous tissue (Fig. 1).

The evidence which the x-rays can give in cases of gastric and duodenal ulcer is of two kinds—indirect and direct. The indirect evidence is that afforded by the recognition of the type of stomach—hypertonic, normal or hypotonic—which is present, the existence of spasm in the stomach or duodenum, and the changes in the motor functions which result from reflex disturbances in the activity of the pyloric sphincter. As much of the indirect evidence depends upon the same disturbances in the motor functions of the stomach as those which are the cause of the pain of a gastric or duodenal ulcer, it may be absent if the examination is carried out during a period when the patient is free from abdominal discomfort, and it is always most obvious if pain is actually present whilst he is being observed under the screen.

The direct x-ray evidence of an ulcer consists in the recognition of the deformity it produces in the outline of the stomach or duodenum.

The indirect evidence had been carefully studied before the war, and comparatively little of importance has been added

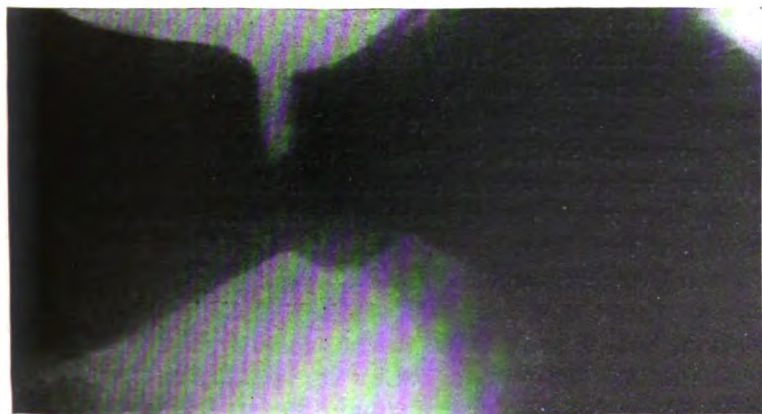


FIG. 1 (a).

Crater of large chronic lesser curvature ulcer, with 25 years' history, forming a tender tumour under left costal margin : spasm on greater curvature (5.12.20).

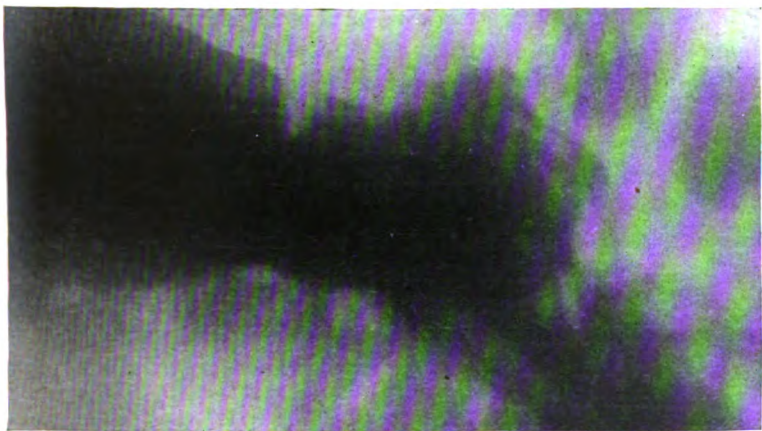


FIG. 1 (b).

Same case as (a) after 1 month's medical treatment. Pain, tenderness and tumour gone. Crater much smaller. Some occult blood still present (2.1.21). Occult blood disappeared after 2 more weeks and crater after 4 weeks.

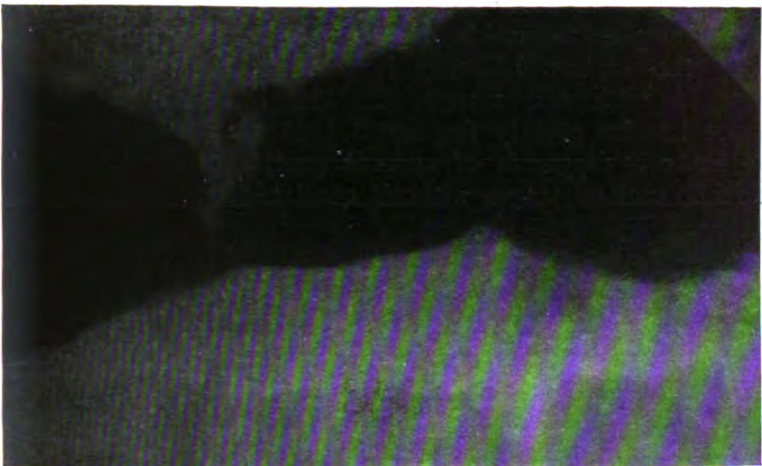


FIG. 1 (c).

Same case as (a) and (b) 3 years later. Patient has remained free from all symptoms during the whole of this period. Crater no longer present. Spasmodic hour-glass constriction apparently replaced by permanent cicatricial constriction, which is insufficient to cause any obstruction (16.1.24).

to our knowledge of it since 1914. At that time, however, apart from hour-glass stomach only the gross deformities produced by the craters of very large penetrating ulcers were recognised with the x-rays. In the last five years the technique has so greatly improved that we would now hesitate to make a diagnosis of chronic gastric or duodenal ulcer even in its earliest stages without confirmation by direct x-ray evidence.

### *Technique.*

Reliable results in the x-ray examination of the stomach and duodenum can only be obtained if great care is taken in the details of the technique. When once a satisfactory method has been established, it should be maintained with as little variation as possible in order that comparable results may be secured. The composition, consistence and bulk of the meal should be constant, the same dose of the same opaque salt should be used, and the examination should be made as early as possible in the morning, when the patient is fasting and not fatigued. This is particularly important in connection with the estimation of the rate of evacuation, which varies greatly under different conditions.

The following description is that of the method we now use as a result of prolonged experience and comparison with the technique of other workers.

It has sometimes been suggested that a patient should be sent to the radiographer for "gastro-intestinal investigation," no note being added as to what disease is suspected. We regard this as very unwise. The exact technique should vary according to the particular condition which is to be looked for. If the clinical evidence is strongly in favour of an ulcer and the first x-ray examination is negative, this should be repeated, if necessary more than once, as in difficult cases a prolonged investigation may be required before direct evidence is forthcoming. The stomach should be washed out and completely emptied an hour before a second examination on another day if the first has been negative, as by this means mucus or even minute particles of food may be removed from the crater of an ulcer, which can then become filled by the opaque meal.

The patient should not take any aperient the day before the examination, but, if he is liable to constipation, an enema may be given the previous evening or in the morning not less than two hours before the examination, and if he has been given medicine containing bismuth, this should not be taken during



the previous forty-eight hours. No drug should be administered during the course of the investigations.

Nothing should be eaten or drunk after nine o'clock on the evening before the examination. If this precaution is not taken, the crater of an ulcer may be filled and the entrance into even a large penetrating ulcer may be blocked by food. The examination should be made as early as possible in the morning with the patient fasting. In ordinary practice the examination is often not made until the middle of the morning, and early tea or even a light breakfast is allowed. This practice is most undesirable, and the better results often obtained in a clinic or hospital are at any rate partly due to the examination being made in the building where the patient sleeps, so that there need be no difficulty about giving the opaque meal at an early hour when he is still fasting.

The opaque meal, which has been found to be most satisfactory for demonstrating small irregularities of the stomach and duodenum and also for filling the appendix, consists of a mixture of four ounces of barium sulphate in warm gruel. The gruel consists of the semi-fluid material left after straining fully cooked quaker oats or oatmeal porridge; it is an excellent medium for holding the barium sulphate in suspension.

The patient is first examined in the erect attitude facing the operator. He is asked to swallow two, three or four mouthfuls according to his density to the rays, and the filling of the stomach is watched. The presence or absence of fluid in the fasting stomach, the position and tone of the stomach, and the speed and depth of the peristaltic waves are judged at this point. The abdomen is then palpated, the opaque meal being manipulated over the surface of the stomach, using as small an opening in the diaphragm of the apparatus as possible, beginning high up in the fundus and slowly working towards the pylorus. Pressure exerted in an inward and upward direction at the lowest part of the lesser curvature easily forces the semi-fluid contents towards the cardiac end of the stomach. By this means any irregularity in the rugæ formed by the mucous membrane of the stomach and the smallest deformity of its outline can be recognised. The patient is slowly rotated in both directions in order to obtain a lateral view of the anterior and posterior surfaces of the stomach. He is now allowed to finish the meal, and the process of palpation is repeated, localised tenderness, lack of mobility, and any irregularity of outline being noted.

Attention is next directed to the filling of the duodenal bulb. It is most important that it should be filled completely,

as otherwise erroneous conclusions may be easily drawn. Constant pressure in an upward direction and towards the patient's right side is applied over the pyloric vestibule, at a point about two inches proximal to the entrance into the pyloric canal. Irregularity of outline, the size of the pyloric canal, and the mobility of the bulb are observed. If the bulb is of the rapidly emptying type, pressure may be exerted by the left hand over the descending part of the duodenum whilst still palpating the pyloric vestibule with the right. This manipulation usually causes the bulb and the part of the duodenum just beyond it to be completely filled. Whilst the bulb is still filled the patient is turned again to his left, so that it may be viewed from a different angle and well away from the spine.

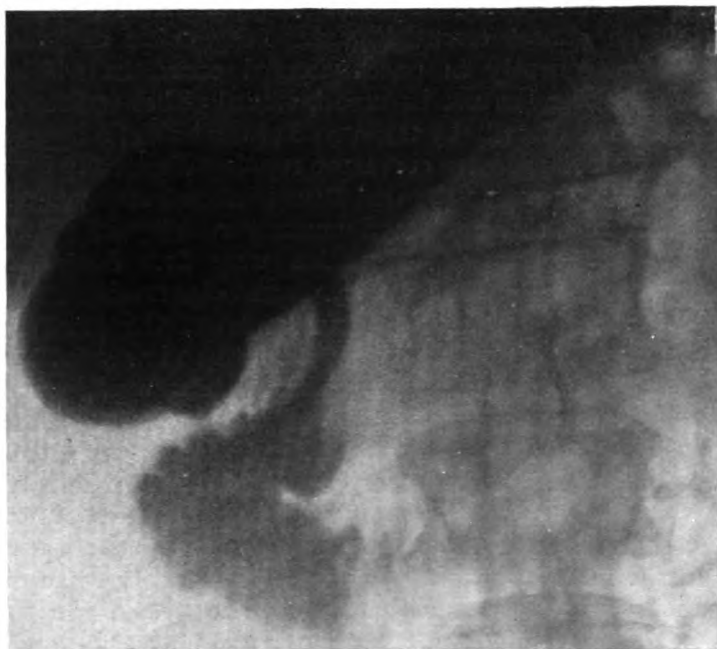
The patient is next examined in the supine position, the outline of the cardiac part of the stomach being observed. If the bulb has not been satisfactorily filled in the erect position owing to functional or organic obstruction of the pylorus, the patient should lie on his right side with his knees drawn up for about five minutes; he is then rapidly turned into the prone position and is again screened. In order that the pyloric vestibule and the duodenal bulb may be viewed from several angles the patient, while lying in the prone position, is rolled first towards and then away from the operator.

Radiograms are taken, if anything abnormal has been observed with the screen, in the position in which it was most obvious, whether erect or recumbent, antero-posterior or semi-lateral. Even if the screen showed nothing obviously abnormal, if a duodenal ulcer is suspected on other grounds, a rapid series of views of the bulb is taken in the prone position in order to record a complete cycle of its filling and emptying. In all cases the exposure should be as short as possible in order to avoid movement.

The patient is examined again at the end of four hours in order to see how much of the meal has left the stomach and whether any abnormalities already discovered can still be recognised. If there is no residue, the patient is given lunch. Otherwise he should fast an additional two hours, when he is again examined for the presence of any residue of the opaque meal in the stomach, or, if the stomach is now empty, in the crater of an ulcer. At the same time the position of the head of the meal is noted, and the appendix can often be seen and examined. The patient may now have a light meal and should continue to eat his usual food and take an ordinary amount of exercise whilst the passage of the opaque meal through the bowels is being watched on the succeeding day or two. During



(a) Duodenal ulcer causing mottled irregular appearance of duodenal bulb.



(b) Same case as Fig. 2 (a), taken during a paroxysm of pain, showing dilatation of pyloric vestibule, which extends so far to the right that it completely hides the duodenal bulb. At the operation a large duodenal ulcer, causing a moderate degree of obstruction of the bulb, was found, and a gastroduodenostomy was performed by Mr. R. P. Rowlands.

FIG. 2.

this time he should take no aperient or other medicine and have no enema. Directly the examination is concluded, he should have a mild aperient, and, if necessary, an enema, in order to get rid of the accumulation of barium sulphate, unless this has been spontaneously evacuated.

#### (A) INDIRECT EVIDENCE

##### (i) *The Tone and Size of Stomach*

(a) *In uncomplicated ulcers.*—The presence of a gastric or duodenal ulcer has no effect on the size of the stomach. Gastric ulcers occur in stomachs of normal size, very rarely in hypertonic stomachs, and quite frequently in hypotonic stomachs. One of us (A. F. H.) has described elsewhere how a hypotonic dropped stomach, such as occurs in women of feeble physique, especially if thin and narrow-chested, predisposes to the development of an ulcer on the proximal part of the lesser curvature. This type of stomach is consequently often seen in women with ulcers of the lesser curvature.

We have also described how the hypersthenic gastric diathesis is an almost essential predisposing cause of duodenal ulcer.<sup>1</sup> Consequently in uncomplicated cases, in which the pyloric sphincter has not become involved either indirectly by reflex action or directly by the spread of the lesion, a hypertonic stomach with the greater curvature running diagonally towards the pylorus high above the umbilicus is almost always present. When this and the associated unusual activity of peristalsis and unusual rapidity of evacuation were first described by Barclay,<sup>2</sup> and confirmed by our own observations, it was thought that they were the result and not the predisposing cause of the ulcer. We now know that this view is incorrect.

(b) *In ulcers complicated by pyloric achalasia and spasm.*—When the evacuation of the stomach is delayed by reflex disturbance in the normal activity of the pyloric sphincter, the tone of the stomach gradually gives way. The pyloric vestibule is the first part to dilate. The dilatation cannot always be recognised whilst abnormally active peristaltic waves are present, but in the intervals, when the waves temporarily cease owing to exhaustion, the stomach can be seen to extend abnormally far to the right, and in exceptional cases even beyond the descending part of the duodenum, as in the case from which the skiagrams shown in Fig. 2 were taken. A chronic ulcer on the posterior wall of the duodenum, which was not actually causing obstruction, but must have influenced the pyloric

sphincter reflexly, was found at the operation by Mr. R. P. Rowlands.

This partial dilatation is a particularly striking feature in cases of duodenal ulcer owing to the hypertonus of the rest of the stomach. It occurs also in pre-pyloric and rarely in lesser curvature ulcers, but as the stomach is already of normal tone or may actually be hypotonic, the additional pre-pyloric dilatation may be difficult to recognise, though an ordinary hypotonic stomach never reaches so far to the right as is observed under these conditions.

At a later stage the functional disturbance of the pyloric sphincter may result in general dilatation of the whole stomach. The characteristic hypertonus is now no longer present in cases of duodenal ulcer; the stomach first reaches the average normal size and then gradually becomes more dilated and hypotonic. But there is nothing characteristic about its appearance. It is, however, important to remember that an originally hypertonic stomach may gradually lose its tone, so that the appearance first described by Barclay as characteristic of duodenal ulcer is not always present, even if no organic pyloric obstruction has developed.

(c) *With gastric and duodenal ulcers complicated by pyloric obstruction.*—The loss of tone of the muscular coat of the stomach and the resulting dilatation, which sooner or later always occur in progressive pyloric obstruction, are easily recognised with the x-rays. The horizontal line, which separates the upper part of the fluid or semi-fluid gastric contents from the gas in the fundus, instead of being situated just below the diaphragm, is abnormally low. In extreme cases it may not reach the lesser curvature: the whole of the opaque meal, together with the accumulation of gastric juice and the residue of food taken the previous day, which were already present when the meal was taken, accumulate in the dependent part of the stomach, the greater curvature of which is very low and may extend into the true pelvis. When this is the case, the exaggerated peristalsis provoked by the pyloric obstruction can do nothing more than give rise to waves on the surface of the gastric contents, which cannot reach the level of the entrance to the pyloric canal whilst the erect position is maintained, so that evacuation only begins on lying down. In such cases the contrast between the extreme degree of atonicity and the over-active peristalsis is very striking, and shows how the two motor functions of the stomach—tone and peristalsis—are entirely independent of each other. The degree of depression of the greater curvature, and especially the distance

between its lowest point and the lowest point of the lesser curvature, give an approximate measure of the extent of the dilatation. This does not vary strictly with the degree of atony, which is measured by the position of the upper level of the gastric contents, because it is further increased by the bulk of the gastric contents still present in the early morning before the opaque meal is taken.

### (ii) *The Peristalsis of the Stomach*

(a) *In uncomplicated ulcers.*—The hypertonic stomach, which predisposes to duodenal ulcer, is associated with very active peristalsis; the waves attain a greater depth by the time they reach the pylorus and they begin nearer the fundus than in the average normal stomach, so that three or four are present at a time instead of two or three.

The inflammatory infiltration of the muscular coat in the neighbourhood of large gastric ulcers interrupts the peristalsis. As, however, the waves are never so obvious on the lesser curvature, where the large majority of ulcers occur, as on the greater curvature, where they are rare, this is not a sign which is often conspicuous. Any considerable interruption in the progress of peristalsis waves as they pass to the pylorus is, in fact, much more suggestive of cancer than ulcer.

(b) *In ulcers complicated by pyloric achalasia and spasm.*—The obstruction offered by achalasia and spasm of the pylorus leads to exaggerated peristalsis, the waves starting further and further towards the fundus, and becoming deeper and deeper as the obstruction begins earlier in the course of digestion, continues longer and becomes less intermittent. Reversed peristalsis, however, is hardly ever observed in the absence of organic obstruction, though we have seen it in one case, in which the disturbance in pyloric activity was a reflex result of chronic appendicitis, no ulcer and no change in the pylorus being discovered at the operation.

Normal peristalsis continues without intermission till the stomach is empty. But exaggerated peristalsis results in fatigue of the muscular coat of the stomach, so that at intervals peristalsis ceases completely. The periods of inertia become longer and more frequent as with increasing obstruction peristalsis becomes more vigorous and more time is required for the evacuation of the stomach.

(c) *In ulcer complicated by pyloric obstruction.*—When the pylorus is directly involved by the pathological changes occurring in the neighbourhood of a gastric or duodenal ulcer, the

obstruction produced is present continuously and not only in the later stages of digestion, as is commonly the case with that caused by achalasia and spasm. Consequently exaggerated peristalsis is seen directly the opaque meal is taken. It begins near the fundus instead of in the centre of the stomach and becomes extremely deep as it passes towards the pylorus. In some cases it is from time to time interrupted by the passage of a wave in the reverse direction: a forward peristaltic wave ceases just before the pylorus is reached and then after a moment passes back as an anti-peristaltic wave. This is very rarely seen except in organic obstruction. The occurrence of violent peristalsis, with or without reversed peristalsis, in a greatly dilated stomach is pathognomonic of organic pyloric stenosis.

The violent peristalsis causes fatigue of the muscular coat, so that periods of hyperperistalsis alternate with periods of complete inertia. In the early stages, when the exaggeration of peristalsis is still sufficiently great to compensate for the increased resistance offered by the pylorus, and in very slowly progressive or stationary cases, in which hypertrophy of the muscular coat has led to more or less complete compensation, there may be few or no periods of inertia, and the time required for complete evacuation is not greatly prolonged. The occurrence of long periods of inertia is a serious sign and indicates that an operation is urgently required in order to prevent the development of complete peristaltic inertia and complete loss of tone, when the risks of gastro-enterostomy are greatly increased.

### (iii) *The Pyloric Sphincter*

(a) *Pyloric achalasia*.—As each peristaltic wave approaches the pylorus in normal individuals, the sphincter relaxes. The relaxation manifests itself on the x-ray screen by the appearance of a fine stream joining the shadow of the extreme pyloric end of the stomach with that of the duodenal cap. In the intervals the pyloric canal is closed, and a clear area occupied by the pyloric sphincter separates the stomach from the duodenum. In some normal individuals the pyloric canal is not completely obliterated by the tone of the sphincter, and an extremely fine shadow traverses the centre of the clear area between the stomach and duodenum. This becomes very much wider and more obvious, when relaxation of the sphincter occurs and gastric peristalsis forces some of the gastric contents into the duodenum.

A duodenal ulcer, and less frequently a gastric ulcer and chronic disease of the gall-bladder and appendix, may reflexly

inhibit this relaxation. The absence of relaxation, or achalasia, of the pyloric sphincter can at once be recognised with the x-rays by the fact that only a certain proportion of the peristaltic waves are followed by the passage of opaque chyme into the duodenum. In most cases of this kind evacuation takes place in a normal manner at first, but after a time, and especially if the patient is experiencing pain, an increasing number of waves end fruitlessly. The result is that the chyme which has been carried by a peristaltic wave towards the pylorus is thrown back as an axial reflux stream.

(b) *Pylorospasm*.—Under the conditions just described it is generally possible, by exerting pressure upon the pyloric vestibule, to force some of the opaque chyme through the pyloric canal into the duodenum, showing that the sphincter, though unrelaxed, has not undergone any increase in its normal resting tone. But occasionally nothing can be forced through, and in such cases it may also be impossible to squeeze anything through during the periods of inertia, which succeed periods of exaggerated peristalsis, though as a rule no difficulty is experienced in doing this. When the pylorus offers an abnormal resistance of this nature, spasm of the sphincter is probably present. The absolute proof of this is obtained by making frequent examinations in order to determine whether the obstruction is intermittent, as it is in pylorospasm, or permanent, as it is in organic obstruction. In most cases the ordinary routine examination gives the required information, as both achalasia and spasm are very rarely present whilst the meal is being taken and for the first few minutes afterwards. If, therefore, evacuation takes place in a normal manner at first, but ceases at a later stage, and if direct pressure cannot then overcome the resistance at the pylorus, spasm is certainly present.

(c) *Organic pyloric obstruction*.—No change in the behaviour of the pyloric sphincter can be recognised with the x-rays in the earlier stages of pyloric obstruction. When the obstruction becomes more severe, the pyloric canal forms a thinner shadow than usual when the barium-containing chyme passes through it, and the channel may be distorted, being neither straight nor centrally situated. When the obstruction is still more severe, nothing can be seen actually passing through the canal, as the quantity of the opaque meal which can be expelled at any time through the very narrow channel is too small to throw a shadow. Consequently the duodenal bulb is never full and does not become clearly visualised; it may even completely escape recognition.



In contrast with what occurs in obstruction due to achalasia, but not with that due to spasm, pressure upon the pyloric vestibule does not force any additional quantity of the gastric contents through the pylorus.

The appearance described is constant from the time the meal is taken until the stomach is empty. In this way it contrasts with the generally delayed and always intermittent obstruction caused by achalasia and spasm of the pyloric sphincter.

#### (iv) *Rate of Evacuation*

The x-rays only give reliable information as to the rate of evacuation of the stomach if the radiologist always uses the same technique. The opaque meal, which should be constant in size and composition, must be taken fasting, and nothing should be eaten or drunk until the time is reached, which is regarded as the limit of the period within which the evacuation of a normal stomach should be complete. With the technique already described six hours is taken as the limit, as it is rare for even a trace of the opaque meal to be present in the stomach after six hours. As an average normal stomach is empty in three or four hours, a preliminary examination is made after four hours, so that, if the stomach is already empty, fasting need not be prolonged by an additional two hours.

(a) *The initial examination.*—At the initial examination it should be noted how quickly the opaque meal passes into the duodenum. In the hypersthenic stomach associated with duodenal ulcer the initial rate of evacuation is considerably greater than the average. It is still more rapid in the "leather-bottle" type of cancer of the stomach, which can, however, be at once recognised by the complete absence of peristalsis, the extreme rapidity of evacuation being due to the infiltration of the pyloric canal making it patent though rigid, so that the gastric contents run out of the stomach as quickly as they enter.

It is a curious fact that in a condition which differs so greatly from the hypersthenic stomach as constitutional achlorhydria, the x-rays appearance should sometimes be almost indistinguishable. The peristalsis may be equally active and the stomach equally hypertonic, but the pyloric canal appears to be continuously patent instead of only opening when peristaltic waves approach it.

If nothing is seen to pass into the duodenum during the first examination, organic pyloric obstruction should be sus-

pected, if peristalsis is abnormally active. If, however, peristalsis is feeble or absent, the delayed evacuation is probably caused by inhibition of peristalsis and of pyloric relaxation, probably due to emotional disturbance, such as the fright caused by the examination in an exceptionally nervous patient and distaste for the opaque meal. If this is the case, the inhibition is generally only temporary, and complete evacuation occurs within the normal time. If, however, definite stasis is discovered in such a case, the examination should be repeated on another day.

(b) *After four hours.*—Most of the contents of the stomach should be evacuated at the end of three or four hours. In cases of duodenal ulcer, in which pain is absent and no reflex disturbance of the pyloric sphincter is present, the stomach is generally empty by this time, and if earlier examinations are made it is often found to be already empty in an hour or an hour and a half.

If a large proportion of the opaque meal is still in the stomach after four hours, it is probable that either functional or organic obstruction is present. If at the first examination evacuation was found to be occurring with the usual or more than the usual rapidity, but an unusually large quantity is found to be present after four hours, the delay is probably due to the occurrence of reflex achalasia and possibly spasm of the pyloric sphincter, especially if at the time of this second examination evacuation is intermittent or has temporarily ceased.

(c) *After six hours.*—The six-hour examination only gives reliable information if the patient eats and drinks nothing after the opaque meal. He should be allowed to sit up or take a little gentle exercise whilst waiting. A very small quantity of the opaque meal still present in the stomach after six hours may be ignored, unless the initial evacuation was very rapid, in which case it may be assumed that some reflex disturbance of the pyloric sphincter has occurred.

If a quarter of the opaque meal is still present after six hours, organic obstruction should be suspected, and if a half or more the diagnosis is extremely probable. A definite diagnosis cannot, however, be made on this evidence alone; the activity of peristalsis, and the behaviour of the pyloric sphincter also require consideration. In any doubtful case, especially if peristalsis has throughout been feeble, the examination should be repeated on another day.

If the stomach is very low in the erect position and the duodenum does not drop with it, the obstruction may be due to the drag of the dropped stomach causing a kink at the point

where the duodenum becomes retroperitoneal and more or less fixed. If this seems a possible explanation, the examination should be repeated the next day with the patient lying on his right side during the six hours following the meal. If gastropptosis is the cause, the stomach is then able to evacuate the contents completely within the normal period.

(d) *After twenty-four hours.*—The additional information, which would be gained by keeping the patient without food or drink for a still longer period when a considerable residue is

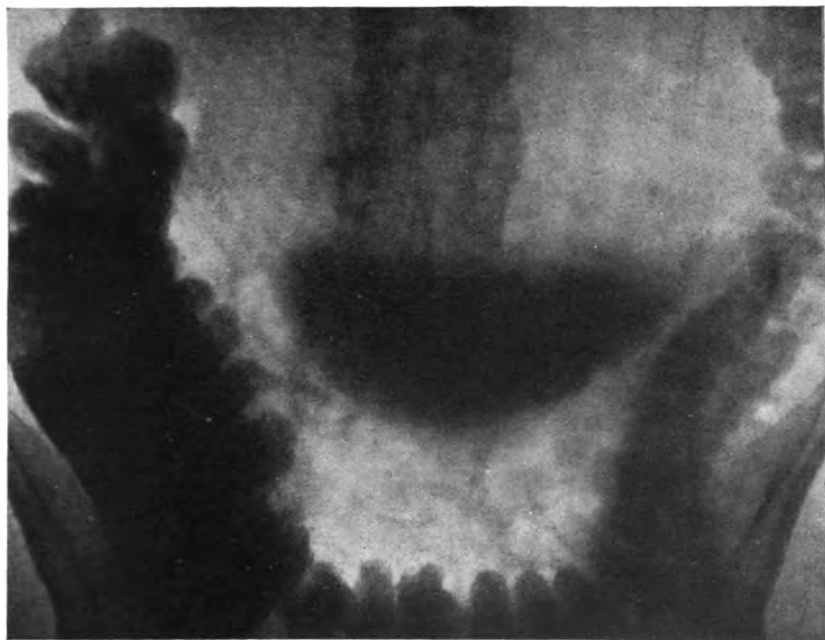


FIG. 3.

Pyloric obstruction due to duodenal ulcer, taken 24 hours after opaque meal to show large residue still in stomach, the remainder of the opaque meal being in the colon. Complete relief by gastro-enterostomy by Mr. R. P. Rowlands.

present in the stomach at the end of six hours, is not of sufficient importance to warrant the discomfort which would result. The patient can therefore take his usual meals after the first six hours.

The presence of any of the opaque meal in the stomach twenty-four hours after it is taken is almost conclusive evidence in favour of organic pyloric obstruction (Fig. 3). The larger the residue, the more complete is the obstruction. Obstruction sufficiently great to cause any considerable residue to remain in the stomach after twenty-four hours is an urgent indication for

early operation. Very small feeds should be taken by mouth, fluid should be given by rectum and perhaps subcutaneously, and the stomach should be thoroughly washed out at night during the short time which may elapse between the x-ray examination and the laparotomy.

(v) *Gastric Contents when Fasting*

Before the opaque meal is begun the patient should be screened in the upright position, and the arrival of the first two or three mouthfuls in the stomach should next be watched. By this means a rough estimate can be made of the bulk of the gastric contents when fasting, if the patient has not had

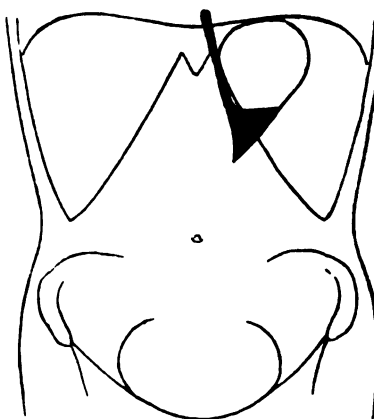


FIG. 4.

First mouthfuls of opaque meal entering empty stomach when fasting in the morning.

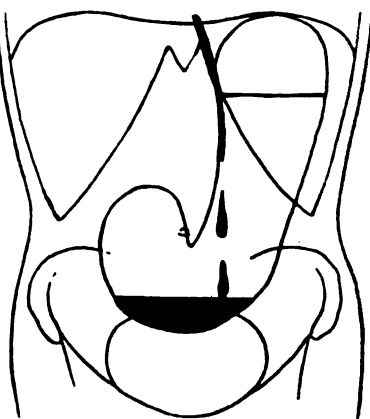


FIG. 5.

First mouthfuls of opaque meal, taken when fasting in the morning, entering stomach already distended with a large quantity of gastric juice as a result of continuous hypersecretion.

anything to eat or drink since the previous evening. In normal individuals and in patients with a gastric or duodenal ulcer which has not directly involved the pyloric canal, no collection of fluid can be seen under the bubble of gas in the fundus, and the first part of the opaque meal is seen to run down the inner side of the pear-shaped cavity, which comprises the entire lumen of the empty stomach, till it reaches the lowest point, from which it passes slowly—often only after a further quantity has arrived—through the previously obliterated lumen of the body of the stomach to the pyloric vestibule (Fig. 4).

When, on the other hand, pyloric obstruction has led to

the constant presence of a considerable quantity of gastric juice—the condition known in Germany as Reichmann's disease and sometimes incorrectly referred to as continuous hypersecretion—the horizontal upper surface of the fluid contents of the stomach can be easily seen below the gas in the fundus. If there is any doubt about this the patient should shake himself, when splashing can be observed. If the opaque meal is now taken, it is no longer held up in the pear-shaped fundus, but can be seen to drop through the fluid already in the stomach to the most dependent part (Fig. 5). The appearance is quite characteristic of the dilated stomach caused by pyloric obstruction. Even in extreme degrees of atonic dilatation, apart from pyloric obstruction, there is no similar collection of fluid in the fasting stomach: the opaque meal drops directly to the most dependent part, but through an empty relaxed stomach and not one which is already partially filled.

By this means it is possible to diagnose organic pyloric obstruction, but it is impossible without the aid of the stomach tube to decide whether the contents of the fasting stomach are pure gastric juice, as they are in the early stages of obstruction caused by an ulcer, or a mixture of much gastric juice with more or less food, as they are in the later stages, or food and mucus with little or no gastric juice, as they are in cases of obstruction caused by cancer.

#### (vi) *Gastric and Duodena! Spasm*

The significance of spasm of the stomach in connection with gastric ulcer and its diagnosis was discussed in a paper on hour-glass stomach published by one of us (A. F. H.) with Mr. R. P. Rowlands in the *Reports* for April, 1921. The diagnosis of duodenal spasm will be discussed in the section on the direct x-ray evidence of duodenal ulcer.

#### (vii) *Localised Tenderness*

There has in the past been much discussion as to the cause of the deep tenderness with which chronic gastric and duodenal ulcers are often associated, especially if pain is present at the time the examination is made. Investigations with the x-rays have proved conclusively that the point of maximum tenderness is almost invariably situated over the ulcer itself. Before recent improvements in technique had made it possible to visualise the large majority of ulcers under the screen, the evidence was less conclusive. It was found that the tenderness was strictly localised to a small area, perhaps on the lesser

curvature or in the bulb of the duodenum, and that this area remained the same, however its position in relation to the anterior abdominal wall might vary with changes in posture or by moving the part involved by deep palpation with the other hand. It was therefore believed that the tender area was actually the seat of an ulcer, and in cases in which an operation was subsequently performed this was generally discovered to be the case.

Since it has become possible to visualise even small ulcers of the stomach and duodenum, it has been found that the actual ulcer is almost invariably the point of maximum tenderness. It is very unusual to find an ulcer which is not tender whenever it is examined, although ordinary palpation may have failed to reveal any tenderness at all. The failure is due to the fact that the tender area is frequently strictly localised to the often small and deeply seated ulcer, which may be so freely movable that it is likely to be displaced during deep palpation, unless this is done under the visual guidance afforded by the x-rays.

The tenderness is so constant that its absence over a suspected ulcer should raise doubts about the diagnosis. The most common causes of confusion are the irregularity in the duodenal outline caused by adhesions secondary to external disease, especially of the gall-bladder, and that caused by the irregular contraction of the fibrous tissue formed in the process of healing of an ulcer which is no longer active. As a rule, neither of these is tender.

The accurate localisation of a tender point to the right of the epigastrium with the x-rays is often of great help when there is doubt between a diagnosis of duodenal ulcer and gall-bladder disease. Although the gall-bladder is almost always further to the right or higher than the duodenal bulb, the position of both is too inconstant for a decisive opinion to be given in difficult cases unless the latter is visualised with the aid of the x-rays.

When at the first examination no ulcer is seen in a suspected case, careful palpation in the most likely parts of the stomach or duodenum may reveal a small area of tenderness. This not infrequently leads the radiologist to the discovery of a small ulcer crater, which might otherwise have been missed.

When an ulcer gives rise to reflex pyloric achalasia or spasm, the extreme pyloric end of the stomach is often tender as well as the ulcer itself, though generally to a less degree: this is due to the increased internal pressure and consequent increased tension on the gastric wall in this situation caused by the closed

pylorus. For some obscure reason there may also be some general tenderness along the lesser curvature of the stomach, wherever the ulcer is situated, but exactly similar tenderness is often observed in the complete absence of all organic disease.

The dilated duodenum caused by partial obstruction at the duodeno-jejunal flexure by the superior mesenteric vessels, which is sometimes a predisposing cause of duodenal ulcer, with which it may therefore be associated, is generally accompanied by diffuse tenderness over the whole duodenum, which is most marked in the part immediately proximal to the obstruction. This condition was described more fully in a paper by one of us (A. F. H.) in the *Reports* for October 1922.

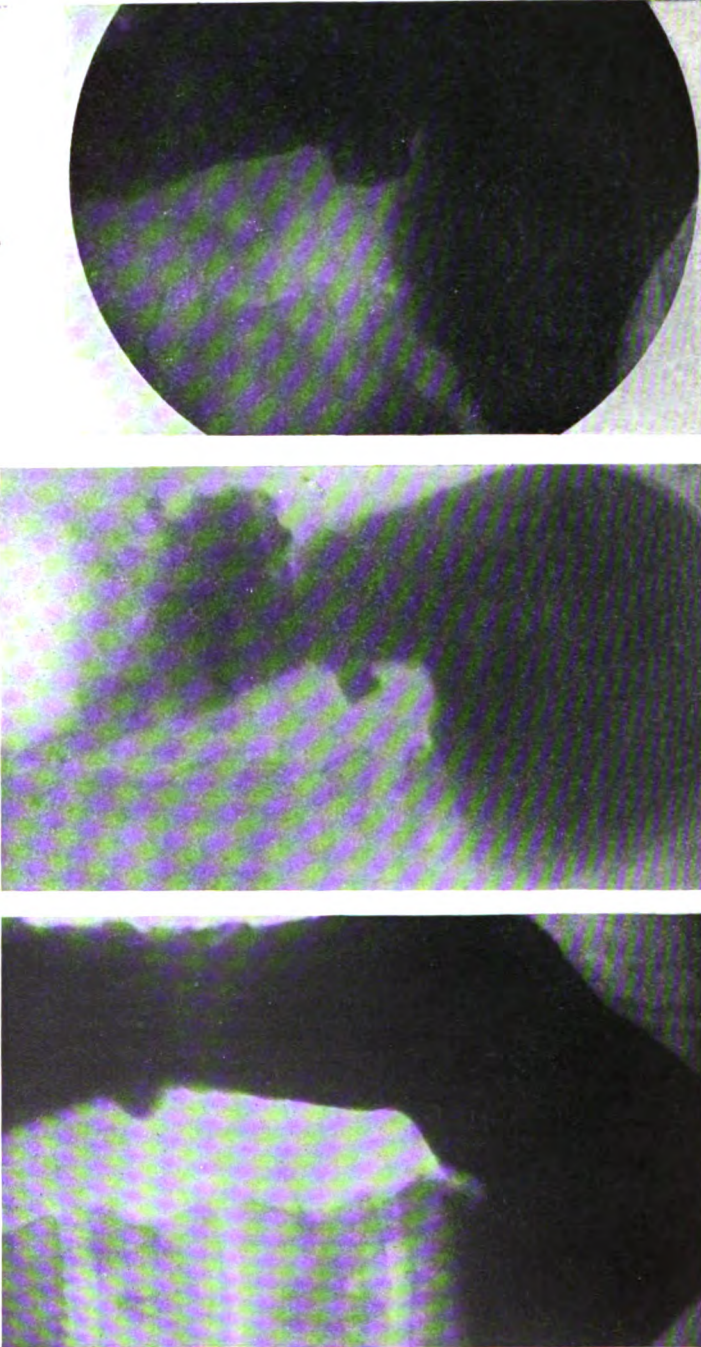
### (B) DIRECT EVIDENCE

The craters of very large gastric ulcers form such obvious shadows with the x-rays after an opaque meal that they can be easily recognised on the fluorescent screen. It was not, however, until the method of taking a series of skiagrams immediately after each other was introduced by Cole, and the newer method of manipulation whilst screening after a very small quantity of the opaque meal had been eaten was introduced independently by Scott<sup>3</sup> and by one of us (P. J. B.), that it gradually became recognised that every chronic gastric ulcer and duodenal ulcer, however early and however small, gives direct x-ray evidence of its presence. It is simply a matter of technique, experience and skill, which determine what proportion of ulcers a given observer recognises. Nobody who is specially engaged in the kind of work should be satisfied with less than a hundred per cent. of successes—though it is hardly likely that any radiologist will attain this ideal until some more years have elapsed.

In every case a screen examination should be made first, and a series of films should be taken of any part of the stomach or duodenum, the appearance of which is suspicious. If the screen has shown nothing suspicious, then a series of films should be taken of any area which has been found to be the seat of localised tenderness, and also of any area which the clinical picture has suggested as a likely position for an ulcer.

#### (i) *Gastric Ulcer*

When the crater of a large and deep ulcer on the lesser curvature penetrates through the stomach wall, it may communicate with a cavity in the pancreas or left lobe of the liver or one situated below the liver and surrounded by adhesions.



(c)

(b)

(a)

FIG. 6.  
Craters of large chronic gastric ulcers in different parts of lesser curvature.

Such an ulcer forms a very characteristic appearance, first described by Haudek <sup>4</sup> in 1913 as a “niche” or “diverticulum,”



which is immobile on palpation (Fig. 6). It often contains a hemispherical gas-bubble above the opaque salt, which may remain in the niche after the rest of the stomach is empty (Fig. 8). The niche is often associated with a drawing in of the greater curvature, causing an hour-glass contraction (Fig. 7).

The crater of a large ulcer, which does not penetrate beyond the stomach, is also easily seen with the screen. It differs

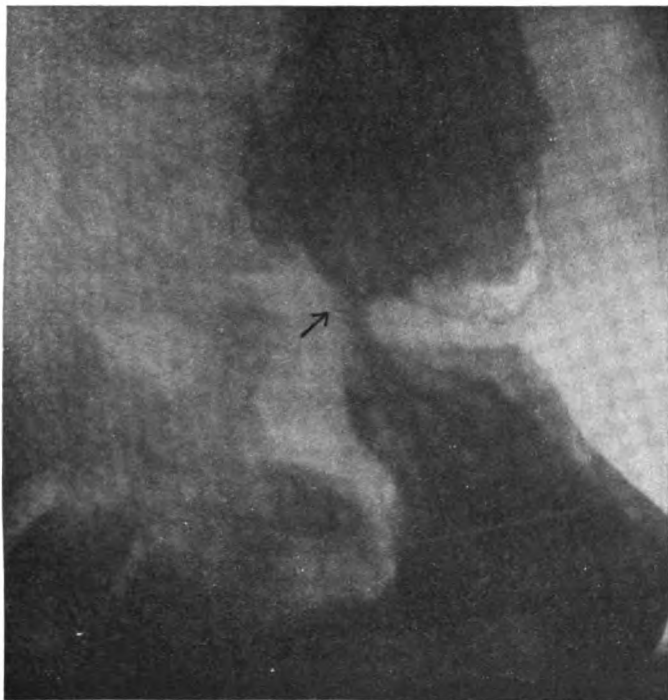


FIG. 7.

Crater of small gastric ulcer, shown on lesser curvature of stomach, leading to hour-glass contraction. Complete recovery followed gastro-gastrostomy by Mr. L. E. Bromley.

from the type of ulcer just described in forming a shallow crater, which is less frequently fixed; it does not expand into a "niche," and it therefore never contains a gas-bubble and is less likely to retain some of the opaque meal after the rest of the stomach is empty.

Smaller chronic ulcers give similar appearances, but after their detection on the screen a series of four skiagrams immediately after each other should be taken of the suspected area in order to determine whether the irregularity which has been seen is constant. The smallest ulcers of this kind have only



FIG. 8 (a).

Lesser curvature ulcer with large crater: stomach filled.

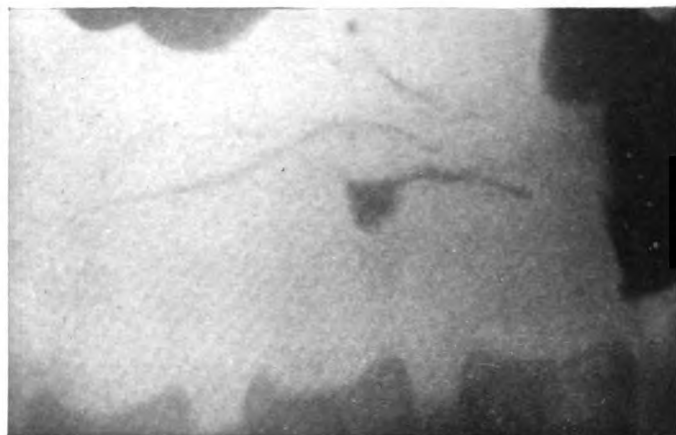


FIG. 8 (b).

Same case as (a), after almost complete evacuation of stomach.



FIG. 8 (c).

Same case as (a) and (b), after 2 months' treatment. Crater now greatly reduced in size: no pain, tenderness or occult blood.

been recognised with the x-rays since the war, largely owing to the work of Cole,<sup>5</sup> who with "serial radiography" has found them far more frequently than all other kinds put together, though this would not be the experience of most surgical clinics. Some are seen best in the erect position, others in the horizontal. The majority can also be detected on the screen by

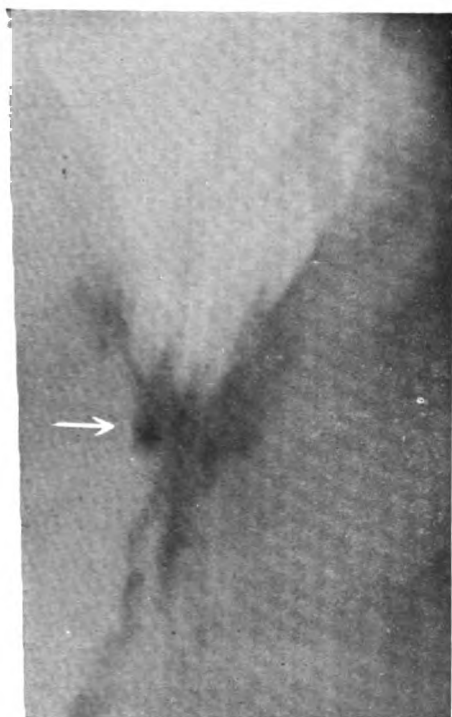


FIG. 9 (a).

Crater of small ulcer on lesser curvature, only visible with a very small opaque meal.

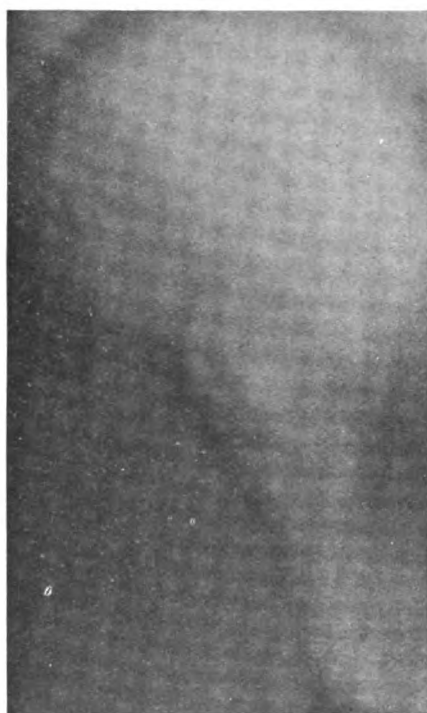


FIG. 9 (b).

Same case as Fig. 9 (a) after 2 months' medical treatment. Crater (together with pain, tenderness and occult blood) completely disappeared.

Scott's method with a very small quantity of the opaque salt in the stomach (Figs. 9 and 10), but a few can only be seen when the stomach is full. In many cases an oblique view reveals an ulcer, which cannot be seen in the direct antero-posterior position.

In very rare cases a small congenital diverticulum situated in the immediate neighbourhood of the cardia may so closely simulate the appearance of a niche, produced by the crater of a large chronic ulcer, that a mistaken diagnosis is likely to be made unless the possibility of this source of error is borne in

mind. This condition will be described more fully in a paper to be published in the October number of these *Reports*.

(ii) *Duodenal Ulcer*

The duodenal bulb is so small in comparison with the stomach that the effect produced upon its shape by the crater of



(a)

(b)

FIG. 10.

Small gastric ulcer on lesser curvature.

(a) Before treatment: arrow points to barium-filled crater.

(b) After medical treatment for 1 month. Crater disappeared together with pain, tenderness and occult blood.

the ulcer with its swollen edges, by the contraction of scar tissue, and by spasm gives rise to a most confused picture (Fig. 11). In the stomach confusion may occur between the results of contraction of scar tissue and of spasm, but the deformity produced by the ulcer itself is quite distinct from these, and is generally situated on the opposite curvature. The result is that in

many cases of duodenal ulcer it is quite impossible to determine what part each of these three factors plays in the production

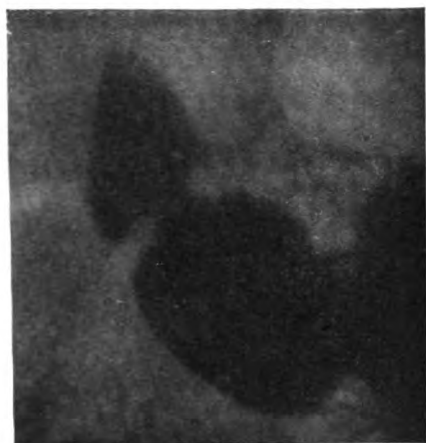


FIG. 11 (a).

Radiogram of normal duodenal bulb.

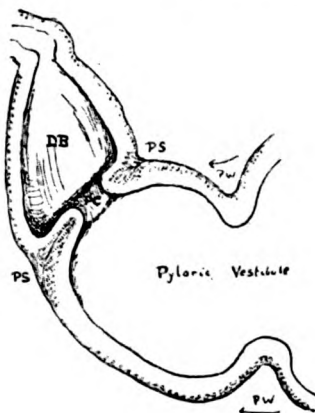


FIG. 11 (b).

Section through normal duodenal bulb, DB, shown radiographically in (a). PS, pyloric sphincter; PC, pyloric canal; P.W., P.W., peristaltic wave passing towards pylorus.



FIG. 11 (c).

Very deformed duodenal bulb caused by duodenal ulcer.

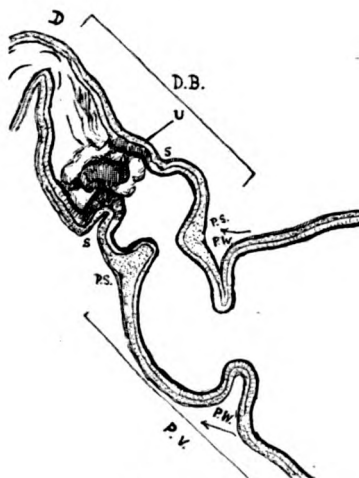


FIG. 11 (d).

Section through duodenal bulb, D.B., shown radiographically in (c), to show deformity caused by ulcer, U, and spasm, SS.

of a deformed duodenal bulb, although the total effect may be so obviously abnormal that a diagnosis of ulcer can be made without further hesitation. The recently published investiga-

tions of Åkerlund<sup>6</sup> of Stockholm have, however, made the differentiation of the results produced by the different factors much less difficult (Fig. 12a). Åkerlund has shown that the "niche" formed by the crater can be recognised much more frequently than was formerly believed; it was present in over 60 per cent. of a consecutive series of 100 cases of duodenal ulcer examined by him with the x-rays. It varies in size from a pin's head to half a walnut. It is more or less rounded, and occasionally an air-bubble is present in its dome. The air-bubble which is occasionally seen at the apex of a normal bulb

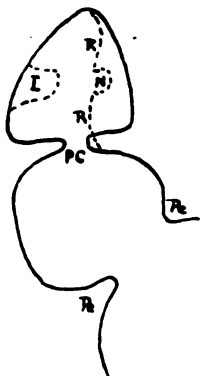


FIG. 12 (a).

Continuous line = outline of normal duodenal bulb. Dotted line = deformed bulb caused by ulcer: N, niche or crater; I, incisura caused by spasm; contraction of fibrous tissue and spasm have caused lesser curvature to become straight, RR, and pyloric canal, PC, excentric. Pe, peristaltic wave passing toward pylorus.

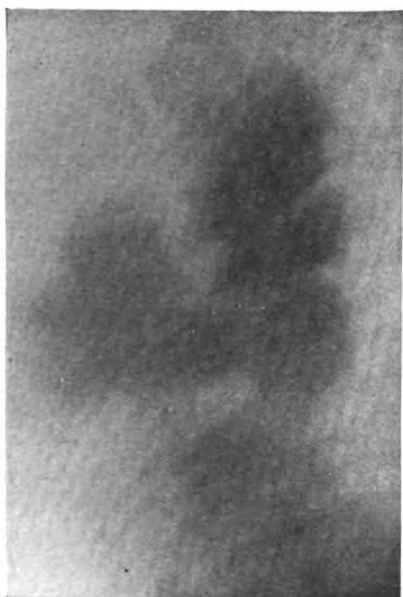


FIG. 12 (b).

Deformed duodenal bulb, with gas-bubble, GB, at apex. PS, pyloric sphincter: DD, descending part of duodenum.

should not be confused with this (Fig. 12b). The majority are seen on the lesser curvature,\* where they appear in profile, even if the ulcer is situated mainly on the posterior or anterior wall. A niche is also sometimes found on the base of the bulb, but very rarely on the greater curvature. In some cases the niche appears as a depression between two projections into the lumen of the bulb, most frequently on its lesser curvature (Figs. 13 and 14), but sometimes on its greater curvature and rarely on its base. These projections represent, we believe, the edges of the ulcer, though it has been suggested that they are caused by a double spasm. If the ulcer is situated entirely on the posterior or anterior surface of the bulb and does not reach either of the

\* It is convenient to refer to the three sides of the triangular duodenal bulb seen with the x-rays as the base, and the lesser and greater curvatures of the duodenal bulb, the latter being continuous with the lesser and greater curvatures respectively of the stomach.



(a)



(b)



(c)



(d)

FIG. 13.

Series of radiograms from a case of duodenal ulcer, showing constancy of deformity of bulb.



FIG. 14.

Chronic duodenal ulcer. Arrow points to barium-filled crater.



FIG. 15.

Large chronic duodenal ulcer, producing partial obstruction of bulb. Complete relief after gastro-enterostomy by Mr. R. P. Rowlands.

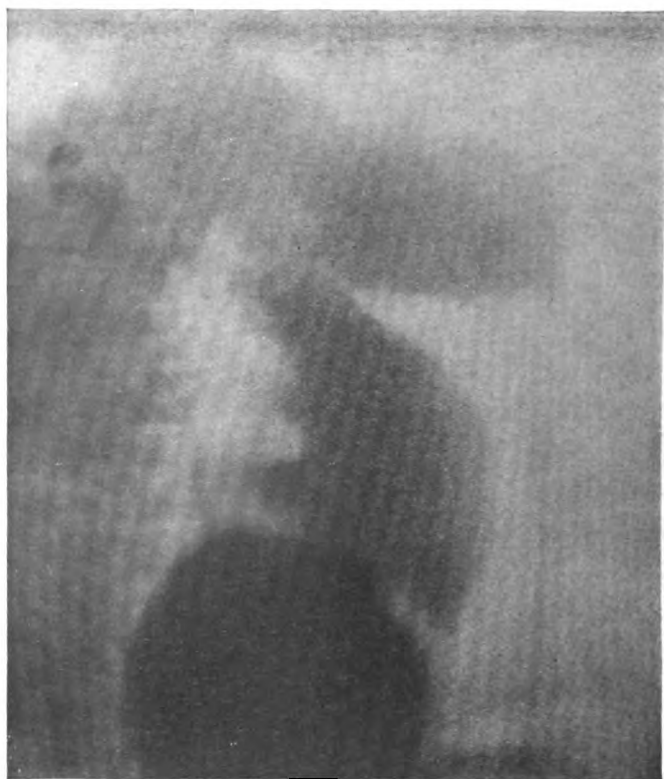


FIG. 16.

Chronic duodenal ulcer.



curvatures or the base, the deformity caused by its crater is almost impossible to recognise, though it may be rendered partly visible by turning the patient round so that the rays pass diagonally through the abdomen. It sometimes gives rise to a dense spot surrounded by the less dense shadow of the rest of the bulb.

Some of the opaque meal is occasionally retained in the crater of the ulcer for some hours after the stomach and the rest of the duodenum have become empty, leaving a small, well-defined shadow in the position of the duodenal bulb. A similar appearance may result from a deposit in the pouch of mucous membrane formed as a result of irregular cicatrisation of an ulcer. Such a residual shadow is of no importance unless it remains on lying down and every trace of the opaque meal has left the stomach, as in normal individuals the duodenum may form a well-defined shadow at the end of gastric digestion, when only a small ill-defined shadow is present in the pre-pyloric part of the stomach or even in the absence of the latter if the erect position is maintained.

A duodenal ulcer very frequently causes a spasm, which is most marked on the side of the bulb opposite to the ulcer, so that the chief effect is seen on the greater curvature when, as is usual, the ulcer involves the lesser curvature. If the ulcer is on the anterior or posterior surface, without involving the lesser curvature, the spasm is likely to produce a depression on both curvatures, an hour-glass bulb being the result (Fig. 15). The depression is shaped like a bite from an apple, being more curved in outline and relatively much wider than the deep but narrow incisura opposite an ulcer on the lesser curvature of the stomach (Fig. 16). It may be so large that it involves the greater part of the area normally occupied by the bulb, but its size varies considerably in the course of a single prolonged observation and at different examinations. A similar spasm may occur in the duodenal bulb as a reflex result of gall-bladder disease and even appendicitis.

The contraction of fibrous tissue in connection with a duodenal ulcer produces a degree of deformity quite out of proportion to its extent owing to the small size of the bulb, the symmetrical outline of which is broken by a very slight amount of fibrous contraction, which would not produce any trace of deformity in the stomach. It is difficult to lay down any rules as to the nature of the deformity produced in this way. It makes the deformities produced by the ulcer crater and by spasm more irregular than they would otherwise be. In a large majority of cases it produces, as Åkerlund was the first to point out, a shortening of the side of the bulb in which the

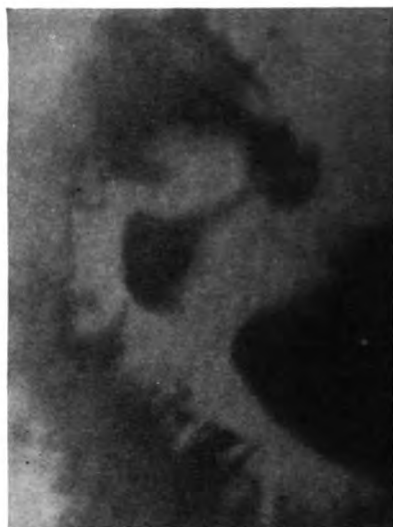


FIG. 17.  
Chronic duodenal ulcer.



FIG. 18.  
Chronic duodenal ulcer.



FIG. 19.  
Duodenal ulcer with considerable deformity of duodenal bulb, together with deformity in pre-pyloric region, probably due to adhesions but possibly to a second ulcer, in a patient who had twice been explored for duodenal ulcer, which the surgeon failed to find. The symptoms were typical, hyperchlorhydria with delayed evacuation was present, and occult blood was found in the stools.

ulcer is situated, so that it becomes straight or even concave instead of convex, and the pyloric canal then joins the bulb excentrically instead of in the centre—generally nearer the lesser than the greater curvature, as the former is the one chiefly involved in the majority of cases. Fibrous contraction may also produce a diminution in the total size of the bulb (Fig. 17), converting the convex outline of both of its curvatures into straight or concave outlines (Figs. 18 and 19), so that the lumen of the bulb may finally be represented by nothing more than a small rounded shadow or a narrow irregular channel

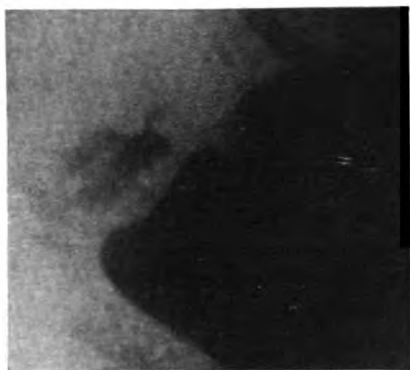


FIG. 20.  
Chronic duodenal ulcer.



FIG. 21.  
Deformity of duodenal bulb caused by pressure of an enlarged gall-bladder.

continuous with that of the pyloric canal, the junction being marked by a sudden change in direction. Beclère<sup>7</sup> has pointed out that deformities caused by fibrous contraction and inflammatory infiltration are rigid, the affected part of the outline showing a loss of its normal suppleness on palpation.

It is quite impossible to form any estimate as to the size of an ulcer from anything about the appearance of the duodenal bulb except a definite niche, as a very small ulcer may cause much spasm, and an ulcer which has almost healed may have led to great deformity by contraction of scar tissue (Fig. 20).

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## INSULIN TREATMENT OF DIABETES MELLITUS

By W. W. PAYNE, M.B., Parsons Research Fellow, and Medical Assistant, Guy's Hospital.

IN this paper on the Insulin Treatment of Diabetes Mellitus it is proposed to deal mainly with the method at present used, and to outline the reasons and investigations which have led to their adoption.

### CHOICE OF CASE

All cases of true diabetes mellitus are treated with insulin with the exception of a few elderly patients, whose blood sugar can be brought to normal level by moderate restrictions of the diet. The case with which a patient's urine can be rendered sugar-free is no guide to their insulin requirement. In the following two cases the urine was sugar-free on an adequate diet, but the blood sugar in both cases was high, and in both cases 35 units of insulin a day were required to bring the blood sugar to normal level.

*Case 26.*—Ada H., age 44, wt. 84 lb. Basal caloric requirement 1,060 calories.

Urine sugar-free on a diet of carbohydrate 85 gms., protein 64 gms., fat 98 gms., caloric value 1,478. The blood sugar was 0.17 per cent. On a lower diet—carbohydrate 22 gms., protein 60 gms., and fat 102 gms., caloric value 1,246. 35 units of insulin were given before symptoms of overdosage occurred. Blood sugar was then 0.07 per cent.

*Case 7.*—Henry G., age 30, wt. 128 lb. Basal caloric requirement 1,500 calories.

Urine was sugar-free on a diet of carbohydrate 36 gms., protein 72 gms., fat 142 gms., caloric value 1,710. Blood sugar 0.18 per cent. 40 units a day produced no reaction.

The blood sugar on 35 units a day was 0.127 per cent.

### DIET

(a) *Caloric Requirement.*—The caloric requirement of a patient at rest in bed can be approximately calculated from the following tables. The surface area in square metres is obtained from Table I, and the calories required per square metre at various ages are given in Table II. An alternative method is described by Poulton in a recent article.<sup>1</sup>

The figure arrived at represents the minimum requirements

of the “ average normal ” person when no external work is being done. Its main use is to enable an initial diet to be arrived at; it does not afford a reliable guide to the final diet. The final diet, on which the diabetic is to live and work, obviously depends on what work is being done, whether the patient is of an active

TABLE I  
*Surface Area Chart (Du Bois)*

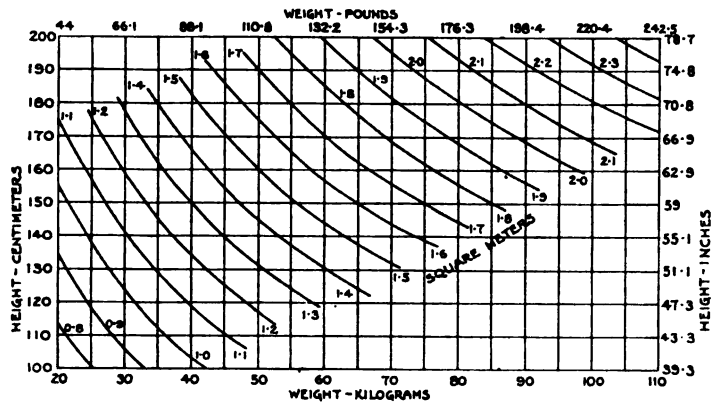


Chart for determining surface area in man in square metres.  
Example: Weight 154.3 lb., Height 70.8 in. = 1.88 sq. m.

TABLE II  
*Caloric Requirement per square metre of body surface (Aub-Du Bois)*

Age.	Males.		Females.	
	Hour.	Day.	Hour.	Day.
10-12	51.5	1,236	50	1,200
12-14	50	1,200	46.5	1,116
14-16	46	1,104	43	1,032
16-18	43	1,032	40	960
18-20	41	984	38	912
20-30	39.5	948	37	888
30-40	39.5	948	36.5	876
40-50	38.5	924	36	864
50-60	37.5	900	35	840
60-70	36.5	876	34	816

or lethargic temperament, and the state of his nutrition, a fat person requiring less per square metre than a thin one. With so many variables the diet cannot be fixed by formulæ. As a rough guide, however, a 50 per cent. increase on the basal requirements is about the maximum allowable.

The ability of the patient to carry on his work (which should not be of a too strenuous nature) without loss of weight is the

best guide as to the adequacy of the diet. A too generous diet will be shown by a steady gain in weight after cessation of the initial rapid gain, which usually follows the commencement of treatment. It should be taken as a guiding rule that a patient should not be allowed to regain the weight he had previous to the commencement of his illness. These considerations, of course, cannot be applied to the growing child. For children formulæ are of but little use; the diet should be the minimum which will allow of normal growth and activity, while keeping the child rather thin.

In severe cases of diabetes a preliminary rest in bed on a "basal" diet is advisable, followed by an increase in the diet as more activity becomes possible. In mild cases this is not necessary, and an initial diet in excess of the basal requirements may be given. The final diet should be fixed if possible while the patient is still under close observation. If in hospital, he should be encouraged to be as active as he is likely to be when he resumes work.

(b) *Protein*.—It is a matter of general agreement that protein in excess is undesirable. The allowance of protein is 1 gm. per kilo. ( $\frac{1}{2}$  gm. per lb.) which is quite sufficient for all bodily needs. This is slightly in excess of the amount allowed by most American writers, who limit the protein to  $\frac{2}{3}$  gm. per kilo. with an increase of about 20 per cent. protein when the patient is doing work.

(c) *Carbohydrate*.—In all young and middle-aged patients, in whom it is important to allow the pancreas the maximal amount of rest, no carbohydrate is added to the diet except as 5 per cent. vegetables, and an occasional grape-fruit, orange or apple. These help in making up bulk. Bread substitutes are usually undesirable owing to their high protein content, while some indeed contain but little less carbohydrate than bread itself. Medolia biscuits and almond bread are exceptions, and bran cakes made with egg-white or agar are a useful vehicle for taking butter at breakfast and tea.\*

(d) *Fat*.—The remainder of the diet is made up as fat, mainly in the form of butter and cream. A fair amount of fat is also included in the usual protein foods.

#### EFFECTS OF EXCESSIVE DIET

(a) *Protein*.—The effect of protein is twofold : (a) it supplies 58 per cent. of its weight as carbohydrate, (b) it increases

\* A convenient list of foods, with their composition and a few recipes for diabetic cooking, by Dr. E. P. Poulton, has recently been published by J. A. Churchill.

metabolism. Extra protein requires extra insulin, but whereas insulin acts within thirty minutes and has lost its effects in about six hours, protein appears to produce its effects many hours after its ingestion. The blood sugar curve taken throughout the twenty-four hours shows peaks after meals, but also shows a rise starting about 8 a.m. and the curve is in all cases still rising when the morning dose of insulin is given. The same rise is also seen when no insulin is taken, but is less marked (Figs. 1 and 2). In comparing the effects of a high and a low protein diet in two patients, it was also noticed that when they were on a low protein diet this early morning rise was later in onset and less in degree.

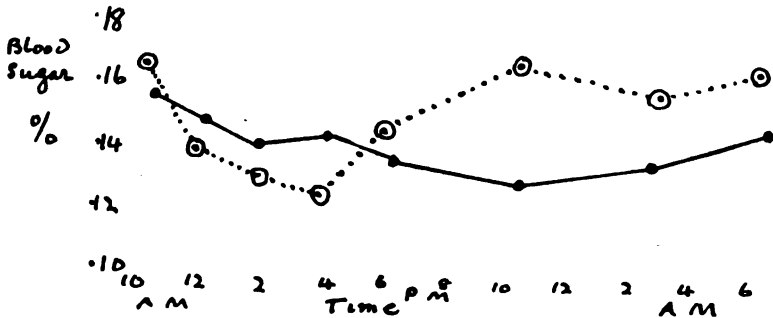


FIG. 1.

Case 25.—Blood sugar during 24 hrs.

Continuous line. On Insulin, 10 units 6 a.m., 15 units noon, 20 units 9 p.m.

Dotted line. No Insulin.

Diet, see Table III. Breakfast, 7 a.m.; lunch, 9.30 a.m.; dinner, 12.30 p.m.; tea, 3.30 p.m.; supper, 6.30 p.m.

As it is impossible to give a large enough dose of insulin to stop this rise without causing a hypoglycæmic reaction, it is necessary to keep the protein low if the blood sugar is to be prevented from rising too high.

(b) *Fat*.—Increasing the fat beyond the amount required to attain the correct caloric intake is not so harmful; but Allen reports that fat, though much less important than the other foods, does increase the blood-sugar level in diabetes, thus requiring more insulin. The effect of fat in increasing the body weight must also be borne in mind. The importance of this will be referred to later.

(c) *Carbohydrate*.—The one evil effect of carbohydrate is the production of a high blood sugar. Marie Hansen<sup>7</sup> has shown that in individual diabetics the rise in blood sugar is proportional to the amount of glucose taken. The effect of carbohydrates other than glucose on the blood sugar rise has

not been studied to any great extent. It had been our custom to allow almost unlimited quantities of "5 per cent. vegetables." The following cases, however, showed that it was not possible to ignore the carbohydrate content of these vegetables.

*Case 33.*—Male, age 18, very advanced diabetic. When having 60 units of insulin and a diet consisting of protein, fat and

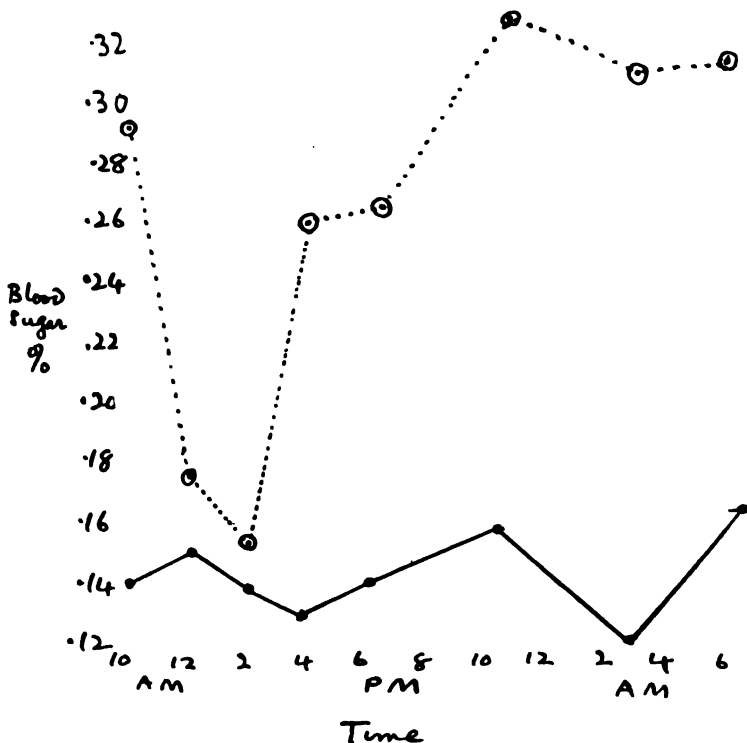


FIG. 2.

*Case 24.*—

Continuous line. On Insulin, 20 units 6 a.m., 25 units 6 p.m.

Dotted line. No Insulin.

Diet, see Table III. Meals as for Case 25, Fig. 1.

32 ozs. of 5 per cent. vegetables, his morning blood sugar was 0.22 per cent. On allowing only 4 ozs. of vegetables, but making no other alteration, the morning blood sugar fell to 0.13 per cent.

*Case 34.*—Female, age 11. Her blood sugar was being followed during the day. At tea-time she had a grape fruit, tea and bran and agar biscuits, carbohydrate content of meal about 20 gms. Her blood sugar, which had been level for two hours at 0.12 per cent., rose to 0.23 per cent., a rise of 0.0055 per cent. per gram of carbohydrate. Previously the effect of glucose 10 gms. and 25 gms. had been estimated. For 10 gms.



the rise was .05 per cent., *i.e.* .0050 per cent. rise per gram, and for 25 gms. the rise was .164 per cent., .0065 per cent. rise per gram.

In Case 34 the carbohydrate of the grape fruit would seem

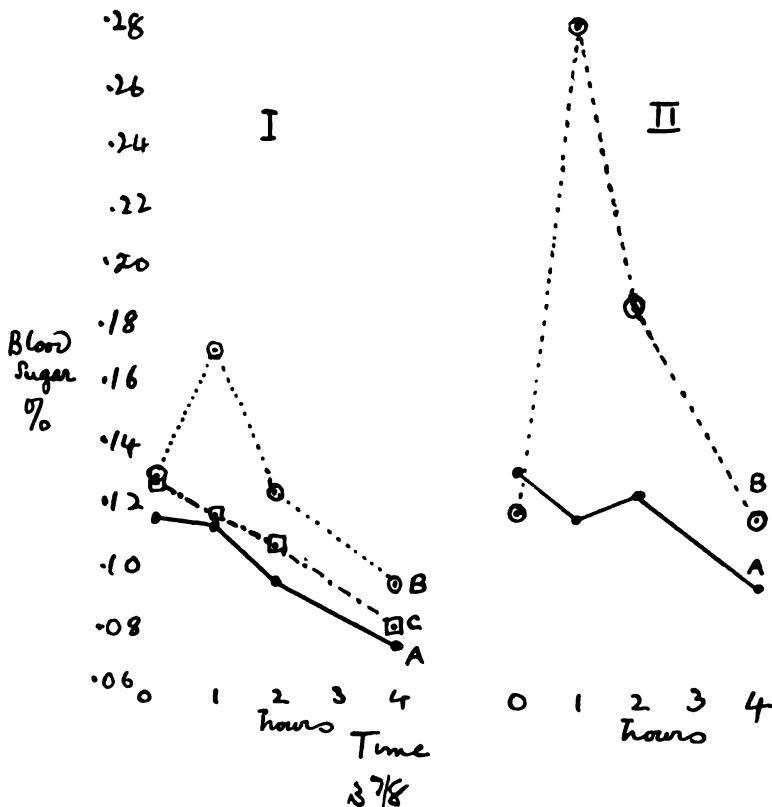


FIG. 3.

I. Case 35.—Insulin, 15 units, and breakfast at 0.

A, 152 gms. egg, 30 gms. fat,  $\frac{1}{2}$  oz. cream, bran and agar cakes; *i.e.* 1 gm. carbohydrate, 17 gms. protein, 54 gms. fat.

B, 32 gms. bread, 48 gms. butter,  $\frac{1}{2}$  oz. cream; bran and agar cakes; *i.e.* 17 gms. carbohydrate, 3 gms. protein, 54 gms. fat.

C, 18 gms. bread, 50 gms. egg, 42 gms. butter,  $\frac{1}{2}$  oz. cream; bran and agar cakes; *i.e.* 10 gms. carbohydrate, 7 gms. protein, 54 gms. fat.

II. Case 30.—Insulin 20 units, and breakfast at 0.

A, 3 eggs,  $1\frac{1}{2}$  oz. butter,  $\frac{1}{2}$  oz. cream; bran and agar cakes; *i.e.* no carbohydrate, 15 gms. protein, 52 gms. fat.

B, 1 oz. bread,  $1\frac{1}{2}$  oz. boiled potatoes,  $1\frac{1}{2}$  oz. butter; bran and agar cakes; *i.e.* 24 gms. carbohydrate, 4 gms. protein, 33 gms. fat.

to be almost equal to an equivalent weight of glucose in raising the blood sugar.

The effect on the blood sugar of the carbohydrate content

of bread, tomatoes, turnips, spring cabbage and Jerusalem artichokes as compared with the equivalent weight of glucose has been studied. The case was No. 16 (Table III), an early and mild case of diabetes. The method adopted was to give a breakfast consisting of the food to be tested together with 76 gms. of egg, 28 gms. butter, 28 gms. bran and agar cake, 14 gms. of cream, and a cupful and a half of tea. No insulin was given. In addition the effect of the meal without any added carbohydrate was obtained. The amount of vegetable used was calculated so as to give 15 gms. of carbohydrate, the figure used being the total carbohydrate less the fibre content as given by Atwater and Bryant.<sup>8</sup> Figs. 4 and 5 show the results obtained, which are summarised in the following table.

Food used.	Weight taken.	Maximum rise of blood sugar.	Rise of blood sugar per gram carbohydrate.	Remarks.
Tomatoes . .	16 oz.	·045	·003	Baked in oven. No loss of carbohydrate.
Bread . . .	29·4 gms.	·052	·0035	Boiled. Some carbohydrate probably lost in cooking. Steamed. Loss of carbohydrate in cooking probably very small. Taken at intervals during the meal in 40 cc. water.
Turnips . .	8 oz.	·028	·0017	
Artichokes .	3½ oz.	·028	·0019	
Cabbage . .	12½ oz.	·044	·003	
Glucose . .	15 gms.	·050	·0033	

Somewhat similar experiments were carried out giving insulin about thirty minutes before the meal. It was found that a dose sufficient to cause symptoms of overdose at the end of four hours was only partially successful in preventing the rise due to carbohydrate. (Fig. 3, I and II.)

Case 35 was a male, aged 45, weight 136 lb., requiring 20 units of insulin a day. Case 30 is referred to later.

It is possible that these transient rises tend to cause further damage to the pancreas. To minimise this, the restriction of carbohydrate to vegetables taken at meals which follow the taking of insulin has been advised. Most diabetics prefer to have their carbohydrate allowance in this manner owing to the greater bulk thus obtained.

(d) *Body Weight*.—Although it is very gratifying to note the increase in weight under treatment, it is not by any means desirable for the patient to increase it up to the weight he had previous to his illness. The increase in weight requires a more than corresponding increase in insulin.

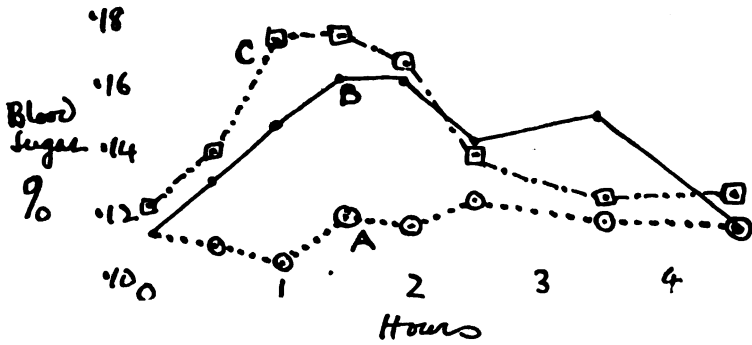


FIG. 4.

Test breakfasts.

A, protein and fat only.

B, tomatoes, protein, fat.

C, glucose, protein, fat.

Case 38 (already referred to) shows this point. On May 10, 1923, his weight was 140 lb., and on 65 units a day his blood sugar was .11 per cent. to .095 per cent. On June 7, 1923, his weight was 149 lb., and on 75 units daily on a diet containing less carbohydrate but otherwise similar his blood sugar had

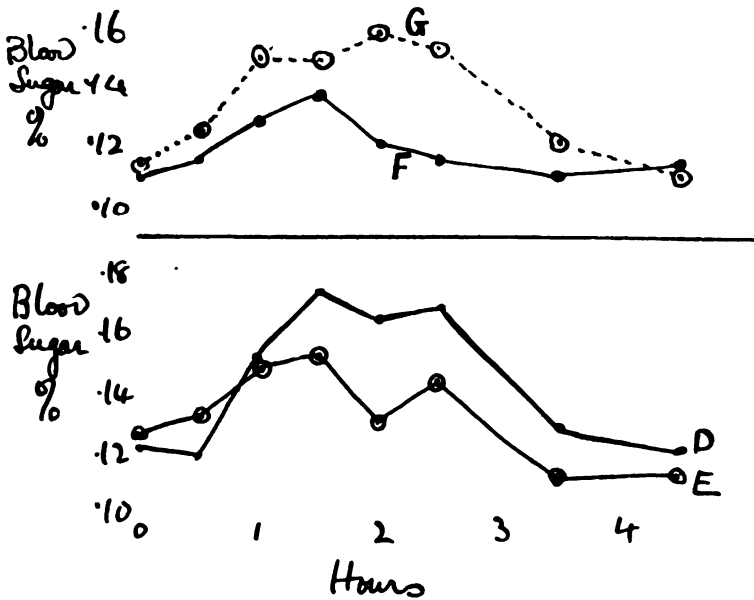


FIG. 5.

Test breakfasts.

D, bread, protein, fat.

E, turnips, protein, fat.

F, artichokes, protein, fat.

G, cabbage protein, fat.

risen to between ·16 per cent. and ·22 per cent. On Nov. 6, 1928, his weight was 151 lb., and on the diet of May 1928, 105 units of insulin failed to cause the blood sugar to fall below ·24 per cent. Thus with an increase of 11 lb. 40 units extra of insulin were required, and even then failed to produce the same results.

### KETOSIS

It has long been recognised that ketone bodies are produced when fat is oxidised in the body without a corresponding oxidation of glucose. Many endeavours have been made to explain this on chemical grounds without any great success. Shaffer<sup>2</sup> appears to be the first to demonstrate by experiment any interaction between glucose and aceto-acetic acid. He found that in the oxidation of glucose by hydrogen-peroxide in alkaline solution, aceto-acetic acid added to the mixture disappeared, and that in optimum conditions (excess of aceto-acetic acid and fair alkalinity) one molecule of glucose caused one molecule of aceto-acetic acid to vanish. Shaffer does not state what happens to the aceto-acetic acid; he was simply unable to recover it from the mixture as acetone. Glycerine lævulose, but not lactic acid, could replace the glucose with equally good results.

Shaffer then attempted to apply this observation to the problem of ketosis in man. He assumed that one molecule of aceto-acetic acid is derived from one molecule of fatty acid. In addition it was found that the leucine, tyrosine and phenyl-alanine fractions of protein formed aceto-acetic acid. Thus protein is able to produce some ketone bodies, and by taking an average analysis of ox-muscle, the ketone-producing power of protein was estimated. That these assumptions are approximately correct is shown by the study of the so-called "absolute" diabetics, in whom practically no carbohydrate is used. (This state of affairs could, of course, only be of very short duration.) It is found that the actual excretion of ketone bodies is very close to the yield calculated from the protein metabolised, as indicated by the urinary nitrogen, and from the fat burned, as deduced from either the caloric production in a calorimeter or the respiratory exchange. That fraction of the diet, which is capable of giving rise to acetone bodies, has been called the ketogenic fraction.

The "antiketogenic" element of the diet, apart from the actual carbohydrate taken, is on a more speculative basis. Protein, when fed to the diabetic organism, yields 58 per cent. of its weight as glucose in the urine, and the glycerin of fat

also yields glucose. Assuming that this glucose formed in the body is of equal efficiency in combating ketogenesis as the ingested glucose, the total antiketogenic fraction is the glucose + 58 per cent. of the protein + 10 per cent. (the glycerin portion) of the fat.

As it was desired to show a molecular relation between the ketogenic and the antiketogenic moieties of the food metabolised, the value of a gram of each food was calculated in terms of milligram molecules of ketogenic or antiketogenic substances that it was capable of producing. For example, the molecular weight of glucose is 180, therefore a "milligram molecule" (or "millimol") will weigh 180 milligrams ( $0.180$  gm.) and thus 1 gm. of glucose will contain  $\frac{1}{0.180}$  milligram molecules of glucose, the antiketogenic substance.

The following table shows the ketogenic and antiketogenic content of 1 gm. of fat, protein and carbohydrate in milligram molecules.

	Ketogenic substance.	Antiketogenic substance.
Carbohydrate . . . . .	0	5.56
Fat . . . . .	3.43	0.56
Protein . . . . .	1.62	3.26

By taking the published figures of many carefully conducted metabolism experiments, Shaffer was able to calculate the amounts of fat carbohydrate and protein actually metabolised by the subject; he then estimated the "ketogenic antiketogenic ratio" at which ketone bodies were excreted in the urine. He found that the ratio was about 1 or just above; *i. e.* when more than one molecule of ketogenic substance was burned for one molecule of antiketogenic substance, ketone bodies were formed. When much ketosis was present, however, there was not a very good agreement between the predicted weight and the actual weight of ketone bodies produced.

In a more recent paper, Shaffer states that he now believes that one molecule of antiketogenic substance can account for two molecules of ketogenic substance.

Wilder and Winter<sup>3</sup> also refer to a series of diabetics, whose ketogenic antiketogenic ratios were frequently as high as 1.7 to 1 with only a faint trace of ketosis.

In the following series of cases under Dr. Poulton's care the ketogenic antiketogenic ratio has been calculated from the diet given over a period of several weeks. It will be observed that a ratio as high as 1.6 has been obtained with no ketosis at all,

and also that ketosis will occur with a ratio as low as 1.0. In every case but two the urine was sugar-free, and most of the carbohydrate was taken as 5 per cent. vegetables. It would appear that the nearer the blood sugar is to normal, the less likely is ketosis to occur. For example, in cases 1, 3, 4, 7, 8, 13 and 18 (Table III), who had at one period slight ketosis and

TABLE III

Case.	Sex.	Age.	Wt. lb.	Diet.			$\frac{K}{A}$	Ketosis.	Method.	Blood sugar %	Remarks.
				C.	P.	F.					
1. P.	F	46	140	50	75	98	0.8	+	Rothera	.16	
2. F.G.	F	45	100	28	65	93	1.0	—	"	.108	
3. H.Q.	M	28	144	32	67	102	1.0	+	"	.09	
4. T.	M	48	120	25	70	107	1.1	+	"	—	At beginning of insulin treatment.
5. S.	F	46	112	42	83	145	1.1	—	"	—	Later with more insulin.
6. C.W.	M	34	128	37	94	155	1.15	+	"	—	Passed trace sugar in urine.
								—	"	.14	No sugar in urine.
								—	"	.17	
7. H.G.	M	30	128	36	72	142	1.2	+	Legal	.18	Ketosis lasted until low blood sugar as shown by overdoses symptoms.
8. A.C.	M	40	126	35	98	160	1.2	+	Rothera	.127	No insulin.
9. W.R.	M	40	112	34	90	160	1.2	—	"	.15	Insulin.
10. C.H.	M	62	136	31	80	147	1.2	—	"	.12	
11. W.F.	M	58	110	31	80	147	1.2	+	"	—	Blood sugar low—symptoms of overdose.
12. H.N.	M	33	134	31	74	131	1.2	—	"	.05	Blood sugar during symptoms of overdose.
13. K.	F	46	140	21	61	101	1.2	+	FeCl <sub>3</sub>	.17	
								—	Rothera	.107	Passing trace sugar in urine.
								—	"	—	No sugar in urine.
15. J.K.	M	32	121	27	66	121	1.2	—	"	.11	
16. R.	M	37	141	26	75	125	1.2	—	"	.09	
17. B.	F	19	80	27	65	128	1.25	—	"	.11	
18. Wil.	M	65	170	16	70	115	1.3	+	"	.13	
								—	"	.15	1½ oz. whisky.
								—	"	.12	
19. J.A.	M	32	118	28	87	162	1.3	—	"	.114	
20. W.B.	M	29	120	14	75	121	1.4	+	"	.17	
21. Ha.	M	56	179	32	81	153	1.4	—	"	.11	
								(±)	"	.13	
22. J.Wr.	M	67	151	22	76	158	1.45	—	"	.15	
								—	"	.10	
								—	"	.16	
23. P.H.	F	28	118	54	82	160	1.0	—	"	—	
				20	78	186	1.6	—	"	—	Insulin 30 units.
				20	94	201	1.6	+	FeCl <sub>3</sub>	—	Insulin on bigger diet decreased to 20 units.
24. Ma.	M	28	170	33	118	275	1.6	(±)	FeCl <sub>3</sub>	.19	Blood sugar range
								—	"	.14	during day.
25. Wa.	M	41	167	31	114	298	1.7	(±)	FeCl <sub>3</sub>	.17	Blood sugar range
								—	"	.12	during day.

Diet is in grams of Carbohydrate (C), Protein (P), and Fat (F).

$\frac{K}{A}$  =  $\frac{\text{Milli-mols Ketogenic substances}}{\text{Milli-mols Anti-ketogenic substances}}$

A = Milli-mols Anti-ketogenic substances.

at another no ketosis with no change of diet, the period of ketosis invariably coincides with the higher blood sugar.

Some American authors, accepting Shaffer's work, have evolved formulæ which give the proportion of carbohydrate, protein and fat in the diet required to produce a ratio of 1 or 1.2 or even higher (Campbell<sup>4</sup>). Recently such formulæ have been used by English writers. It is to be regretted, as rendering

comparison difficult, that some have used as a ratio the weight of fatty acid to the weight of glucose. [Such a ratio divided by 1.5 will give the molecular ratio of fatty acid to glucose.] Thomson,<sup>5</sup> for example, has introduced a new formula ("Thomson's formula"), which aims at a ratio of 2 to 1 (by weight). Except as an exercise in mathematics, such a formula, resting neither on an exact chemical nor clinical basis, is practically valueless.

The use of any such formulæ is not to be advised. They

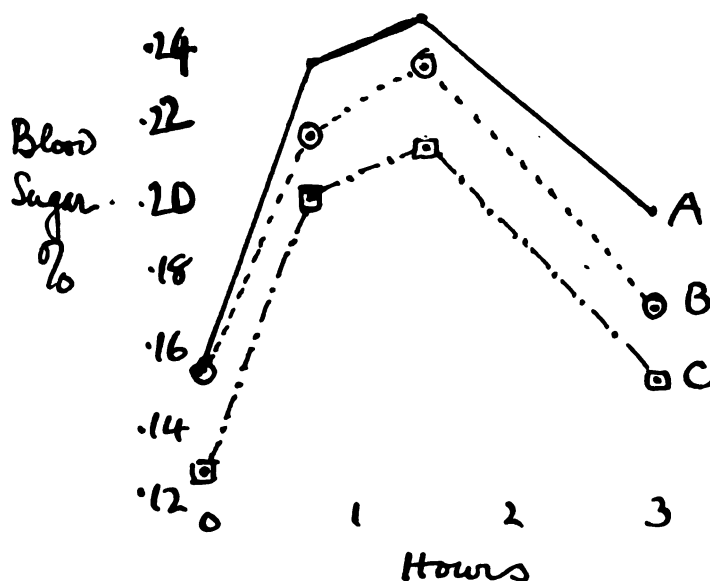


FIG. 6.

Case 27.—Blood sugar after 25 gms. dextrose.

A, before treatment, 15.6.23.

B, after treatment, 10.7.23.

C, at home three months, on diet, 25.10.23.

give an appearance of scientific accuracy, which is not sufficiently supported by evidence, and they also tend to cause an unnecessary rigidity in the diet. It is seen from Table III that the diet is of less importance in the production of ketosis than the patient himself. The surest way of controlling ketosis is to keep the blood sugar within reasonable limits.

#### INSULIN TREATMENT

Our objects in using insulin in diabetes are (1) to enable the patient to use a diet adequate to his needs; (2) to prevent the disease from progressing, and to promote such a degree of recovery as is possible.

The feelings and weight of the patient are a sufficient guide

to the first. The absence of any reliable method of estimating the pancreatic function renders it difficult to assess the results of treatment as to the second object. The response of the patient to a dose of 25 gms. of dextrose as shown by the blood sugar has been used as a rough guide. The sugar was taken after a night's fast, and if the patient had been having insulin it was omitted for forty-eight hours previously. In any one individual the amount of the rise of blood-sugar percentage bears

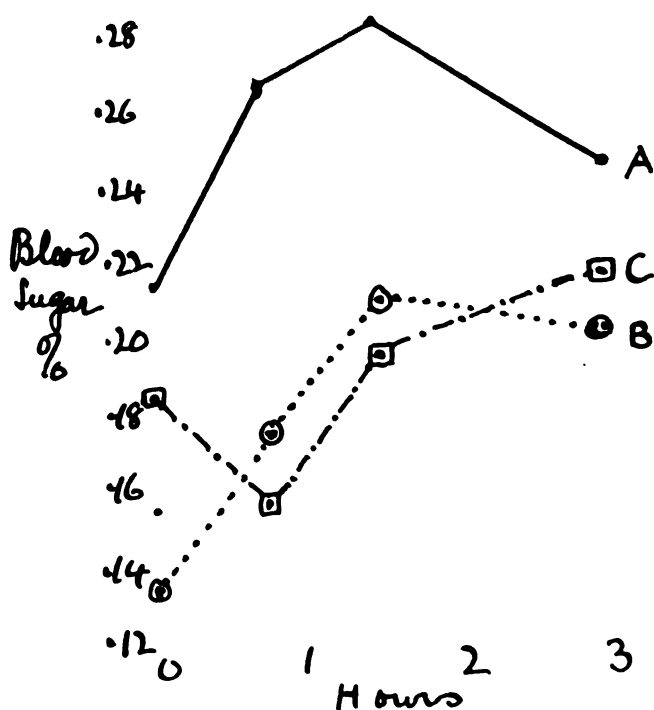


FIG. 7.

Case 25.—Blood sugar after 25 gms. dextrose.

A, before treatment, 31.5.23.

B, after treatment, 4.7.23.

C, after six months at home on diet, 19.1.24.

some relation to the carbohydrate tolerance, but it has not been possible to compare the tolerance of one patient with that of another by means of such curves. It was thought probable that recovery was more likely to occur the nearer the blood sugar was kept to normal. The following cases tend to illustrate this point.

*Case 27.*—Female, age 24, wt. 130 lb., was put on a diet of carbohydrate 33 gms., protein 98 gms., and fat 205 gms., and sufficient insulin to keep her blood sugar during the day just



below 0.1. Fig. 6 shows the tolerance curves (1) before treatment, (2) after one month's treatment in the ward, and (3) after three months at home under similar conditions.

A steady improvement is shown

*Case 25.*—Male, age 41, wt. 167 lb., was put on a diet of carbohydrate 31 gms., protein 114 gms., fat 298 gms. His daily blood sugar on insulin is shown in Fig. 1. Fig. 7 shows his tolerance curve before and after treatment in the ward and six months later.

The initial improvement has been maintained.

*Case 24.*—Male, age 28, wt. 170 lb. Diet carbohydrate 33 gms., protein 118 gms., fat 275 gms. His daily blood sugar on insulin is shown in Fig. 2, and is definitely too high most of the day. Fig. 8 gives his tolerance before and after treatment and shows a loss of tolerance. His diet was reduced to carbohydrate 24 gms., protein 63 gms., and fat 180 gms., on which he experienced frequent hypoglycæmic reactions. He remained on this diet at home with sufficient insulin to be just free of reactions, and after three months the curve shows a definite gain in tolerance.

While these results and also the improved metabolism, as shown by freedom from ketosis, would show that the patient is best off with a low blood sugar, at the same time it cannot be denied that as regards symptoms and weight diabetics having insulin may be practically normal, while having a high blood sugar and passing sugar in the urine.

*Case 28.*—Mrs. M. M. was admitted suffering from extreme weakness and wasting. In the hospital she regained her strength and weight and her urine remained sugar-free on 55 units a day. On going home she took only 10 units a day, and was not as strict with her diet as before. She passed sugar, and her blood sugar was always over 0.3 per cent. She continued to improve clinically, and was able to resume her work. She now states that she feels better than at any time since her marriage. When placed on her original diet her blood sugar when having 30 units a day was as low as when she had 40 units previously; allowing for the alteration in the strength of the unit, this would show that her tolerance had remained about stationary.

However, the balance of evidence tends to show that a low blood sugar is desirable, and in our treatment we have aimed at keeping the patient's blood sugar as low as possible.

To do this it is necessary to arrange the daily time-table in such a manner that the effects of the insulin should as nearly as possible neutralise the effects of the meals. As most of our patients have been taught to give their own injections (Poulton<sup>1</sup>), and are away from home at midday, morning and evening doses only are given. These doses are followed

by the two main meals, between which nearly all the carbohydrate of the diet is divided—usually as tomatoes at breakfast and vegetables at dinner. The midday meal should be of

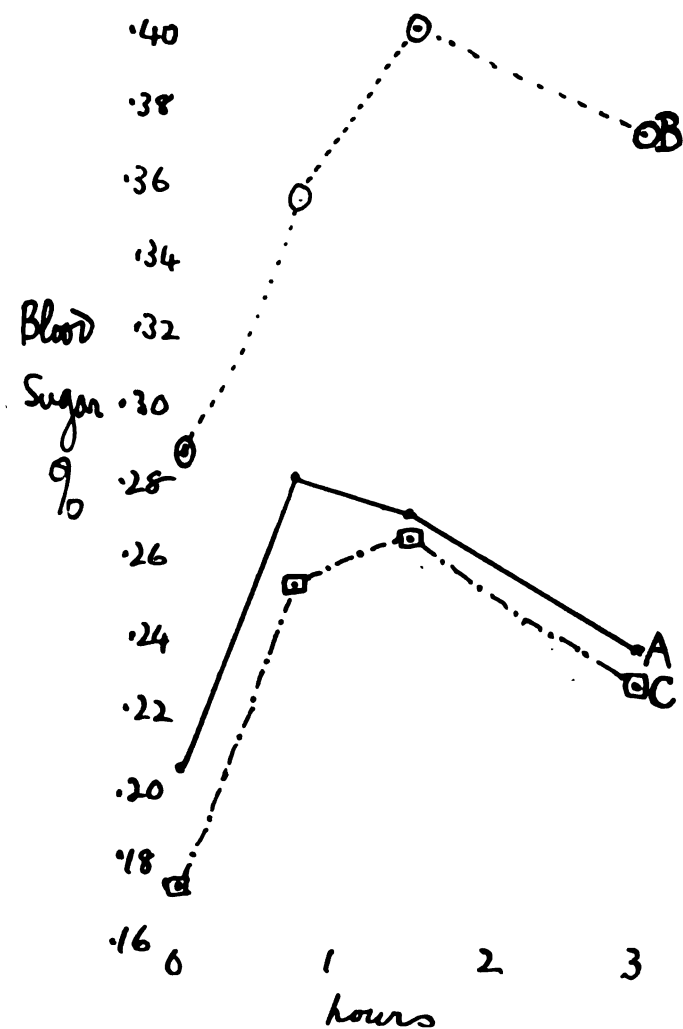


FIG. 8.

Case 24.—Blood sugar after 25 gms. dextrose.

A, before treatment, 31.5.23.

B, after treatment, 4.7.23.

C, after revised treatment and two months on diet at home, 16.10.23.

protein and fat only, this having a minimal effect on the blood sugar. Tea should be very light, but fat can be taken, usually as cream and butter on bran and agar cakes.

Blood-sugar estimations should be done about four hours

after the morning dose of insulin and about one hour before the evening dose, as it sometimes happens that symptoms of overdose occur in the morning, while the afternoon figure is too high.

*Case 29.*—Female, aged 15. She had symptoms of overdose in the morning, and her blood sugar was 0·065 per cent. at 10.30 a.m.; at 5 p.m. it had risen to 0·145 per cent. By rearranging the midday meal and breakfast the symptoms were abolished, and the blood sugar at 10.30 a.m. was 0·08 per cent., and at 5 p.m. 0·115 per cent.

It is usual to give equal doses of insulin morning and evening, but if symptoms of overdose occur regularly after one dose and not after the other, a few units should be transferred.

In starting treatment with insulin, no starvation period is necessary; in fact, the patient is put straight on to the diet already described. A blood-sugar estimation before insulin is started is useful, but it does not afford any indication as to the ultimate dosage required; as in fact we know of no means of foretelling the insulin requirements in any given case, small initial doses are given, gradually increasing them until a satisfactory blood-sugar level is attained. The initial dose is 5 units twice a day, and each day an increase of 5 units is made, the morning dose being increased before the evening dose, until the blood-sugar estimations are satisfactorily low. As the morning figure approaches normal, it is better to make the increases every other day.

Before the final diet and dosage are settled, it is advisable to give the patient a slight overdose of insulin in order to acquaint him with the symptoms. It is important that every patient having insulin should be aware of these symptoms. The more common are shakiness, sweating, hunger, nausea, or a feeling of emptiness, giddiness and dizziness, mental disturbances and headache. This is too long and too vague a list to enable an untrained patient to identify his own symptoms, but once he has experienced it, he will have no difficulty in recognising the onset of a hypoglycæmic reaction, and will be able to take the necessary steps to stop it. Usually a cup of tea or a biscuit is sufficient for this purpose.

Equipped with this information it is quite safe to send the diabetic home on diet and dosage which will keep his blood sugar permanently below about 0·13 per cent. The only other warning should be that unusual and prolonged exercise, such as golf, or as in a recent case, spring cleaning, may cause symptoms of overdosage to arise.

This scheme of treatment requires several blood-sugar estimations to be done. In cases where there are no facilities

for this, an adequate treatment can still be achieved by increasing the dose of insulin somewhat more slowly, say by 2 units a day (5 units is quite safe in hospital), and watching carefully for the first symptoms of overdose. When this point has been reached, the dose is reduced to the previous level and kept there for a few days. Sometimes a reaction occurs at this level, and then a further reduction is made. More often, however, nothing happens, and then the dose should be increased again as before until a reaction occurs again. The final dose settled on is one which is about 5 units less than that required to cause symptoms. Very often after a month it will become necessary to drop another 5 units, possibly owing to increased tolerance. In the earlier cases which showed this the probable cause was, however, the gradual increase of the strength of the unit, in one case in particular the necessity for adjusting the dose occurred only during the period of increase and stopped as soon as the unit was stabilised at its new level.

The following cases illustrate these points.

*Case 30.*—Female, age 16. Blood sugar before treatment .27 per cent. Insulin increased 5 units a day until 25 units were given in the morning and 20 at night. On this she experienced a general shakiness abolished by taking soup. Discharged on 20 units night and morning. Subsequently she had to reduce the dose because of reactions. Blood sugar three months later, 12 noon, 0.10 per cent.

*Case 10.*—Male, age 62. Blood sugar before treatment .29 per cent. Insulin increased 5 units a day until 25 units were taken twice a day. 55 units were given next day as follows : 6 a.m. 25 units; 12 noon, 20 units; 6 p.m., 10 units. Increases of 5 units a day were continued until 65 units were given (25-20-20). A severe reaction occurred the third day on this dose. It was reduced to 50 units (20-15-15), when another reaction occurred. A further reduction to 35 units was made and no more reactions resulted.

Blood sugar at time of first reaction 0.05 per cent.

*Case 26.*—Female, age 44. Blood sugar before treatment .17 per cent. Insulin increased 5 units daily until 35 units a day were given, when symptoms of overdose occurred (depressed—hungry—palpitation).

Blood sugar .073 per cent. On 25 units patient was free from symptoms.

*Case 9.*—Male, age 40. Blood sugar before treatment .28 per cent. Insulin increased by 5 units a day to 30 units twice a day; 65 units a day were next given : 30 units in the morning 20 midday and 15 at night. Symptoms of overdoses resulted from this increase (trembling—headache—dazed—perspiring). The dose was reduced to 30 units twice a day. Symptoms occurred after both doses, further reduction to 55

units was made and slight symptoms were noticed. This dosage was continued, and no further symptoms resulted.

In some cases symptoms are obtained with the first three or four doses. This may be due, not to the correct dose having been reached, but to the depleted carbohydrate reserves of the patient. It was shown in a previous paper<sup>6</sup> that a bigger fall in blood sugar occurred with the same dose in the same patient the day after a fast than when on the regular diet. Under these circumstances as the patient regains weight, it will be found that increasing doses can be tolerated (*vide* Case B.M., reported by Poulton<sup>1</sup>).

In severely emaciated cases this early fall may be so marked that alarming symptoms may result from small doses, and deaths may even occur. In such emaciated cases, glucose should be given after each dose (2 gms. per unit of insulin) until the patient has recovered strength to some extent.

In a few cases symptoms occur before the blood sugar has reached the usual low level. In one case symptoms (headache, tingling of face) occurred frequently when the blood sugar was about 0.16 per cent.; and in two other cases symptoms have occurred when the blood sugar fell to only 0.11 per cent. In the two latter cases the blood sugar subsequently fell to 0.10 per cent. without symptoms occurring. While, therefore, it is possible to treat a case without blood-sugar estimations, it is decidedly preferable to have at least a few estimations done.

#### EFFECT OF INFECTION

*Gangrene.*—In several cases of gangrene in elderly diabetics (all over 60) we have noticed, in common with other observers, that large doses of insulin can be tolerated with but little alteration in the blood sugar.

*Case 31.*—Male, age 66, gangrene of great toe. Urine sugar-free when dieted, blood sugar 0.18 per cent. On 65 units of insulin, blood sugar was 0.12 per cent.

*Case 32.*—Male, age 65, gangrene of toe, amputation, infection of stump, subsequent reamputation. When dieted blood sugar was 0.21 per cent. On 80 units the blood sugar was 0.17 per cent.

In these cases there did not appear to be any greater improvement clinically from the use of insulin than would have been expected in pre-insulin days from the restricted diet on which they were placed. The arterial aspect of the gangrene would seem to be of greater importance than the diabetic.

*Acute Infections.*—The following case illustrates two varieties of acute infection :—

**Case 82.**—Male, age 85. Diabetes of short duration. On 10 units a day blood sugar varied in July 1928 between .09 per cent. and .135 per cent.

On 20.10.28 he was readmitted with a sore throat, which rapidly cleared by 24.10.28. His blood sugar on a similar diet to the previous time with 10 units of insulin varied between .28 per cent. and .34 per cent. on 22.10.28.

On 31.10.28 the blood sugar varied between .09 per cent. and .10 per cent.

In the middle of November his gums became sore and several teeth were found to have apical disease. Three teeth were extracted, and during the following week there was a septic condition of the sockets with some secondary hæmorrhage.

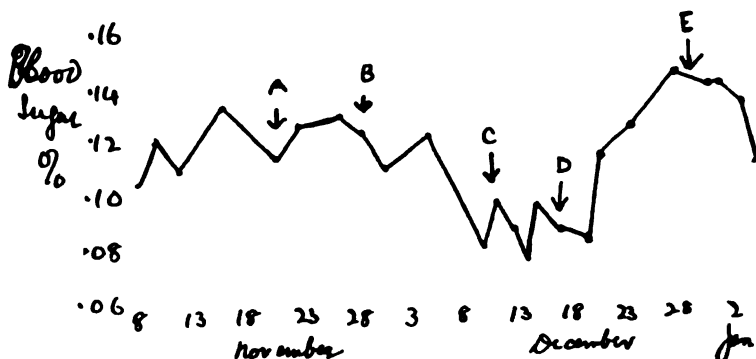


FIG. 9.

**Case 31.**—Effects of Parathyroid.

A,  $\frac{1}{8}$  gr. parathyroid t.d.s. given.

B,  $\frac{3}{16}$  gr. parathyroid t.d.s.

C,  $\frac{3}{8}$  gr. parathyroid t.d.s.

D, parathyroid omitted.

E,  $\frac{3}{8}$  gr. parathyroid t.d.s.

Twelve units of insulin were being taken, but the blood sugar was fluctuating between .31 per cent. and .17 per cent. After the sockets had healed the blood sugar fell to .18 per cent. The next week the gums again became sore, and the blood sugar rose to .17 per cent., falling again to .13 per cent. on improvement.

Similar results have been observed with styes and whitlows. (See Case 2, Fig. 11.)

#### PARATHYROID MEDICATION

With a view to seeing if the theories of parathyroid action would be substantiated by experiment, the effect of combining insulin injections with parathyroid gland by mouth was tried. Four patients were placed on a diet with insulin, and the blood sugar at noon taken daily. Rising doses of parathyroid gland were then given.

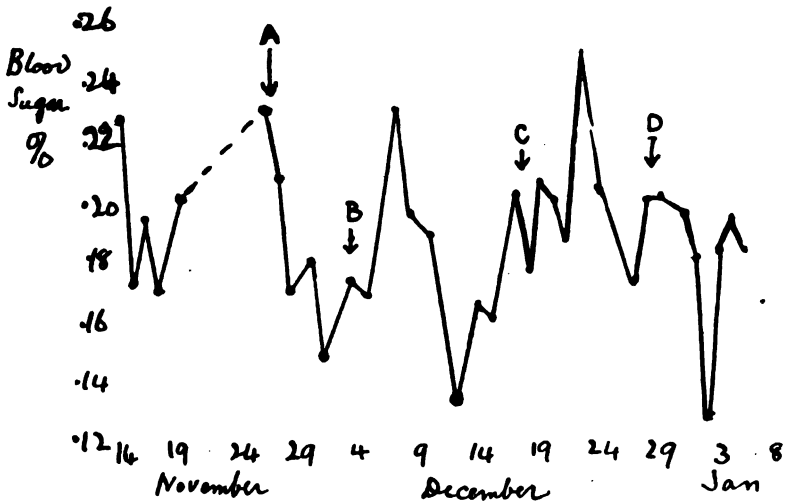


FIG. 10.

## Effects of Parathyroid.

Case 5.—Blood sugar at noon.

A,  $\frac{1}{8}$  gr. parathyroid, t.d.s. given, increased to  $\frac{3}{8}$  gr. on Nov. 28th.

B, parathyroid omitted.

C,  $\frac{3}{8}$  gr. parathyroid t.d.s. given.

D, parathyroid omitted.

The high figure of 22nd December was due to lemon syrup being given in error.

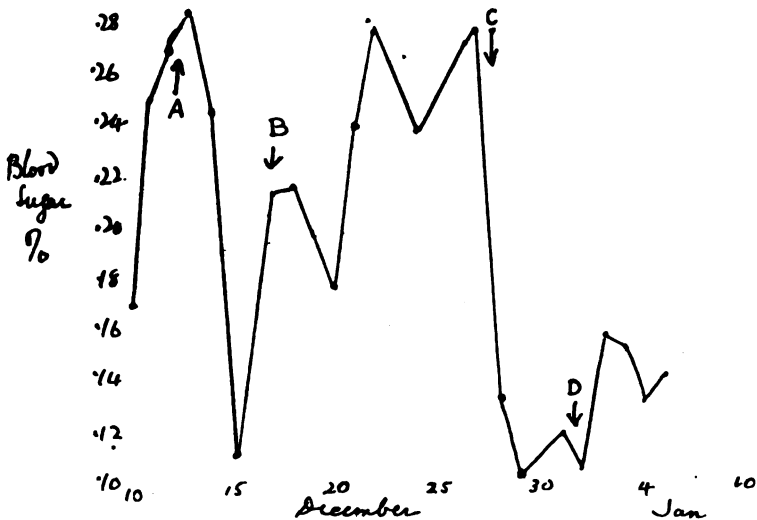


FIG. 11.

## Effects of Parathyroid.

Case 2.—8 units of insulin a day omitted on 10th Dec.

A,  $\frac{3}{8}$  gr. parathyroid t.d.s. given.

B, a sty started in one eye and later the other eye was infected.

C, 12 units of insulin a day extra were given. Reduced next day by 4 units.

D, parathyroid was stopped.

**Case 31.**—Gangrene. No alteration clinically in his condition during period of test (Fig. 9). A definite reduction of the blood sugar followed some days after the parathyroid was started. On omitting parathyroid the blood sugar rose, to fall again on restarting parathyroid.

**Case 5** (Fig. 10).—Very little definite can be obtained from this. In November the giving of parathyroid was followed by a fall of blood sugar, and after omitting the dose a rise occurred. In December a fall of blood sugar occurred spontaneously, and later the effect produced by parathyroid was masked by the accidental giving of lemon syrup. The figures over Christmas are not reliable, as the diet varied. Omitting parathyroid on December 28 appears to have caused a fall.

**Case 2** (Fig. 11).—This experiment was very encouraging to start with, as there was a sharp fall following the parathyroid. The subsequent curve would appear merely to illustrate the effect of styes and insulin. The last few days, however, were again clear of complications, and here the omission of parathyroid was followed by a rise of blood sugar.

The fourth case was No. 82, already referred to, and although prolonged observations were made, it was impossible to obtain any information from the blood-sugar level owing to large and inexplicable variations.

While some of these results distinctly suggest that parathyroid gland has a lowering effect on the blood sugar when given along with insulin, yet the almost opposite results obtained in Case 5 in December render a more definite conclusion impossible.

In conclusion, my thanks are due to Dr. E. P. Poulton, in conjunction with whom most of this work was done. I must also acknowledge my indebtedness to Dr. J. H. Ryffel for much help and for laboratory accommodation, and to Dr. John Fawcett for permission to publish some of his cases.

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# MEASUREMENTS OF THE RED CELLS IN THE ANÆMIAS OF SPRUE AND *DIBOTHRIOCEPHALUS LATUS* INFECTION

By R. D. PASSEY, *M.C.*, *M.D.*, Gull Student, Guy's Hospital, and J. CARTER BRAINE, *M.B.*, Griffiths Demonstrator of Pathology, Guy's Hospital.

(From the Pathology Department, Guy's Hospital.)

IN nearly all the accounts of the anæmias, which accompany sprue and infection of the alimentary tract with the tape worm,

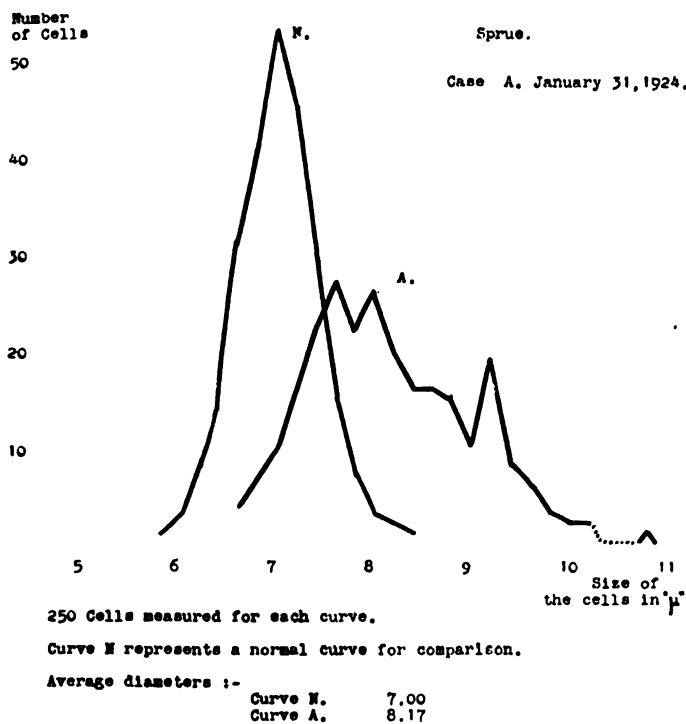


CHART I.

*Dibothriocephalus latus*, it is stated that the blood resembles that found in pernicious anæmia as regards the types of cell, colour-index, and leucocyte count.

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It seemed worth while, therefore, to measure the red cells in these two conditions, to see if they showed the megalocytic phenomenon and the cell-distribution curve, which Price-Jones (1922) <sup>1</sup> has shown to be constant factors in the blood in Addison's (pernicious) anæmia.

Films of five cases of sprue were obtained by the courtesy

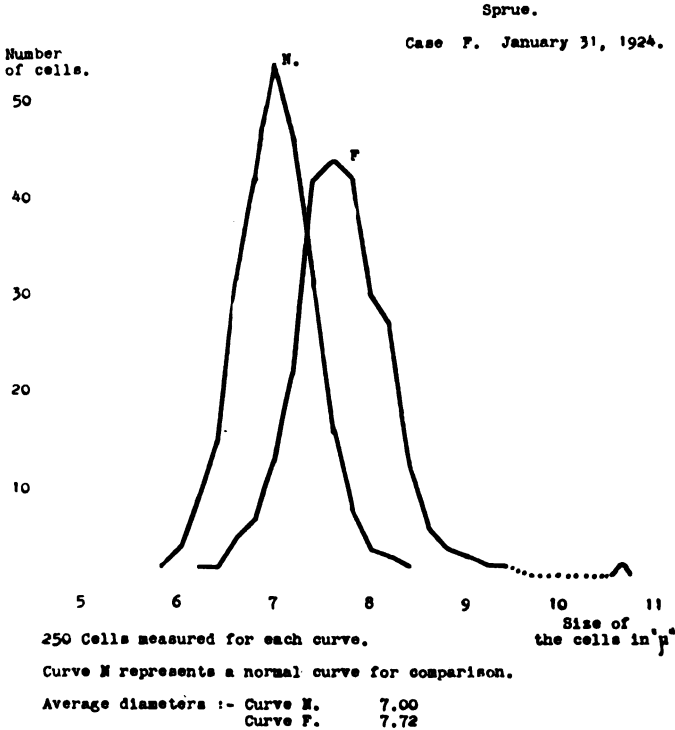


CHART II.

of Dr. G. Low from the Hospital for Tropical Diseases, Endsleigh Gardens.

Measurements of the cells showed that in three out of the five patients there was a definite deviation from the normal. These three cases, A, F and L, had red cells of an increased average diameter, and their cell-distribution curves had moved to the right; so that in these details they may be considered to resemble cases of Addison's anæmia. The average mean diameters were  $8.17\mu$ ,  $7.72\mu$ , and  $7.89\mu$ , respectively, the normal mean—with the method used—being  $7.00\mu$ . The changes in the remaining two, Mrs. H. and B., were slight, so that, for the purpose of clearness in reading the chart, their

graphs have not been included. Their mean measurements were  $7.10\mu$  and  $7.40\mu$ , respectively.

A short clinical history of these cases is given in the Appendix.

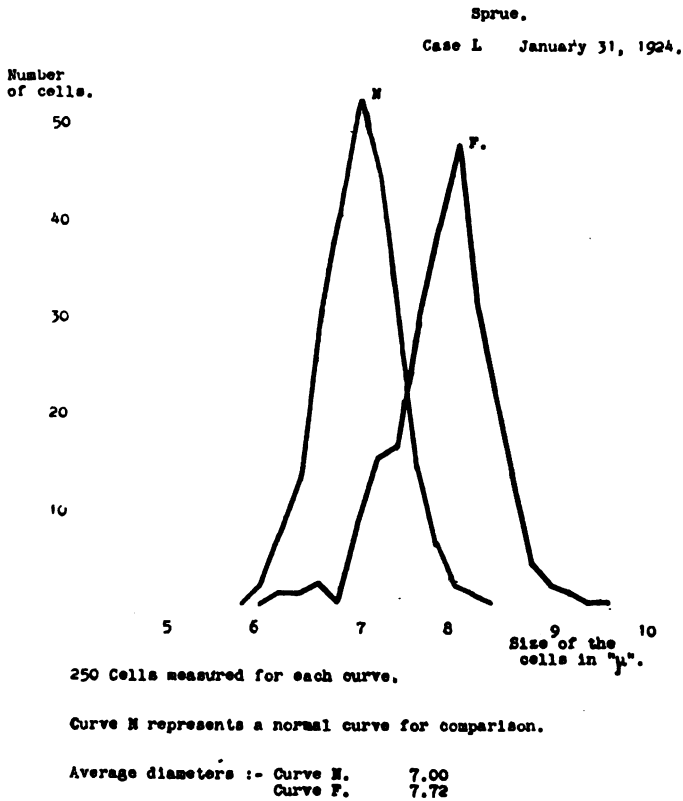


CHART III.

#### *DIBOTHRIOCEPHALUS LATUS* INFECTION

The changes occurring in *dibothriocephalus* infection have been studied in four subjects. Of these, three were infected experimentally by the swallowing of the plerocercoid stage of the parasite, and one by natural infection.

Our thanks are due to Professor Leiper of the London School of Tropical Medicine for his kindness in providing a series of blood films of the three experimental cases, taken at various dates throughout the experiment.

This made it possible to measure the cells immediately after infection, during the experiment, and at the end. In two cases, R. L., and M., measurements were also made some

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time after the termination of the experiment, in the former over a year, and, in the latter, nine months.

Films of the fourth case were kindly supplied by Dr. J. Smith from a patient, an Esthonian sailor from Riga, who was under his care in the City Hospital, Aberdeen. In this instance blood-films obtained thirty-eight days after removal of the worms by treatment were also measured. Unfortunately this case was complicated later by a superadded infection

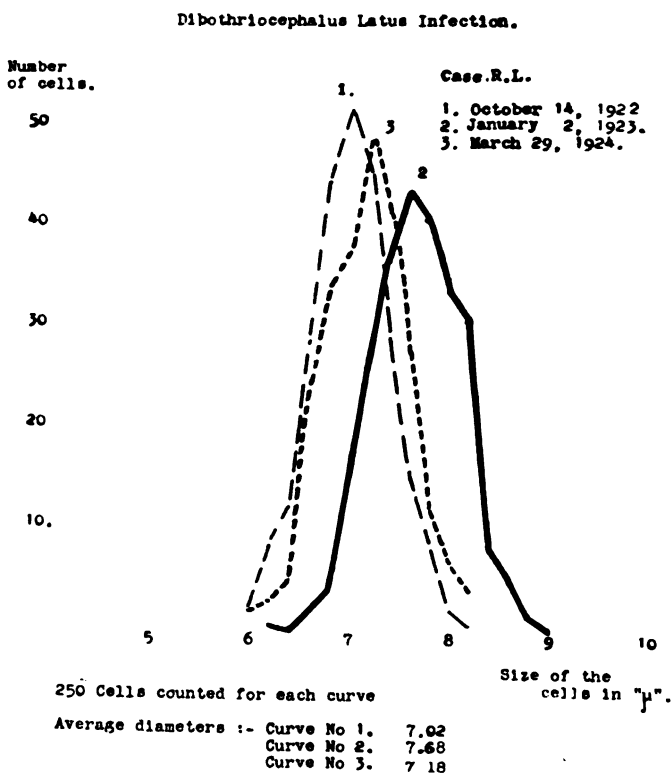


CHART IV.

of typhoid fever, though it is doubtful if this factor would materially alter the size of the red cells.

In none of these cases of dibothriocephalus infection was the anæmia marked. In that of the Esthonian seaman the hæmoglobin percentage was 79, whilst in the three experimental cases the hæmoglobin percentage never fell below 90, treatment being commenced as soon as signs of impairment of health occurred.

It was unfortunate for this experiment that in no case did a greater degree of anæmia result, since, without a greater

destruction of blood, it could not be expected that the red cells would show extreme changes or variations in size. However, in all four cases, the average size of the red cells was unmistak-

*Dibothriocephalus Latus* Infection.

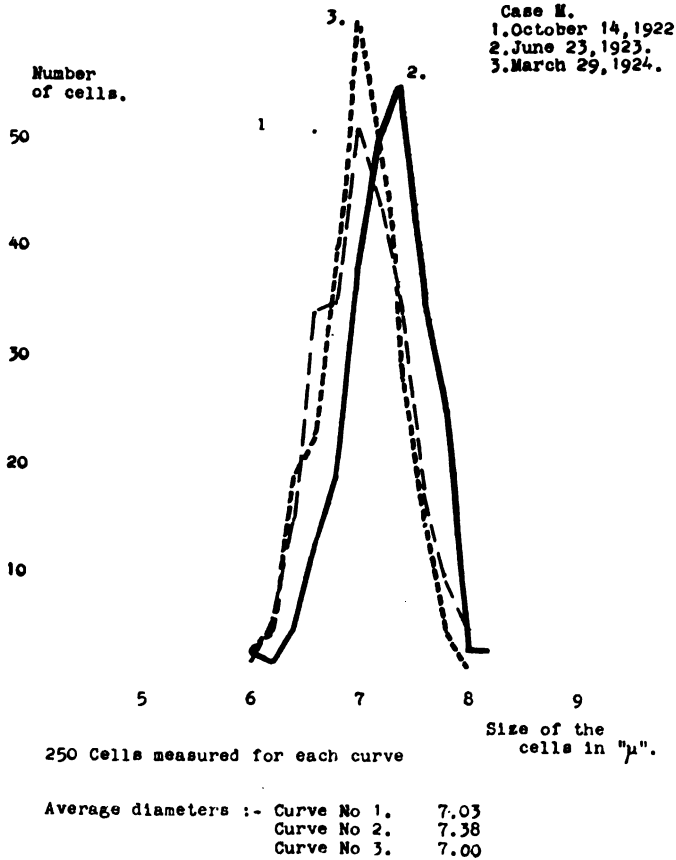


CHART V.

ably increased. In the experimental cases the increase in size at the end of the experiment was as follows :—

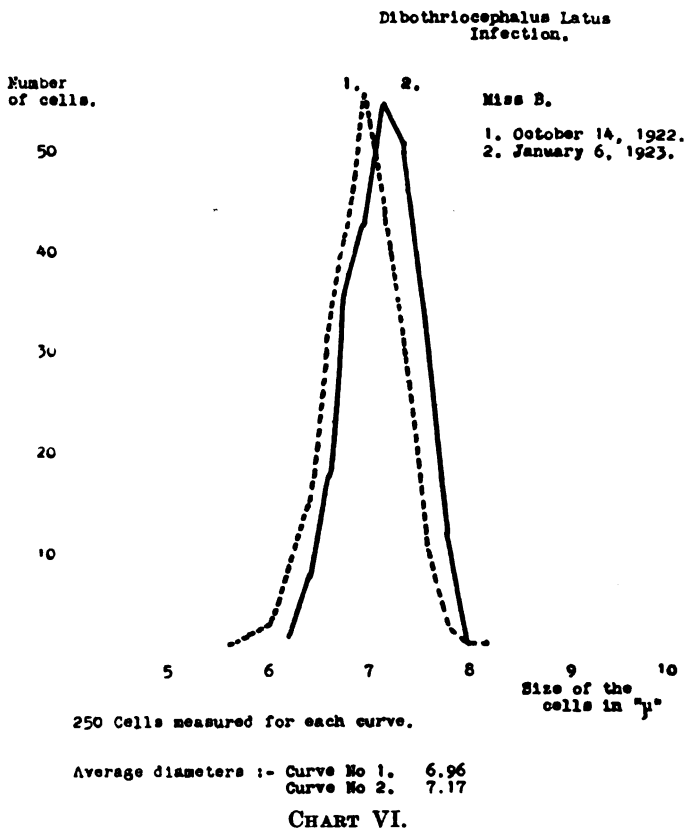
R. L.	from	7.02μ	at the beginning to	7.68μ	at the end		
M.	„	7.03μ	„	„	7.38μ	„	„
B.	„	6.96μ	„	„	7.17μ	„	„

Fifteen months after the termination of the experiment, the cells in the case of R. L. had returned to 7.18μ, and after nine months those of M. to 7.00μ. The red cells of the Estonian, who had a far greater degree of anæmia, averaged

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8.04 $\mu$ ; thirty-eight days after treatment they had returned to 7.66 $\mu$ .

It thus appears that not only does the presence of the worms cause the appearance of a larger type of cell in the blood stream than is found normally, but *vice versa* their disappearance is followed by a return to the normal. This return to the normal after the removal of the infective agent adds emphasis to the

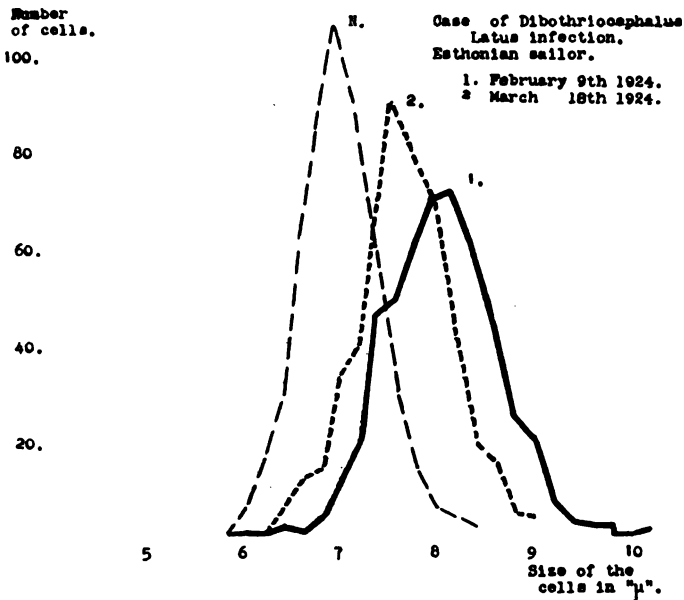


interpretation that the presence of the parasite is the cause of the megalocytosis.

As may be expected from the comparatively mild degrees of anæmia met with, in none of these cases, either of sprue or dibothriocephalus infection, did the blood-films show many changes other than those recorded above. No normoblasts or megaloblasts were seen, nor was poikilocytosis or anisocytosis a feature. Polychromasia and punctate basophilia were absent.

## DISCUSSION

In three out of the five cases of sprue, and in all the four cases where the patients were harbouring the tape worm, *Dibothriocephalus latus*, definite enlargement of the red blood corpuscles was demonstrated, and the cell distribution curves showed some widening of the base of the curve together with a movement towards the right.



500 Cells measured for each curve.

Curve N represents the average of a series of normal curves.

Average diameters :-

Curve N	7.00
Curve No 1.	8.04
Curve No 2.	7.66

CHART VII.

It appears therefore from these few cases that in the diseases under discussion there occur changes in the size and in the distribution curves similar to those found in Addison's anæmia. Moreover, as none of the cases dealt with in this communication would be described from the clinical point of view as severe, it may be anticipated that greater changes will be found in more advanced cases, which will therefore show a greater approximation to the cell-distribution curves in Addison's anæmia. This contention is supported by the investigations of Hampson and Shackle on sprue (1924)<sup>4</sup> and by measurements given by Schauman in his work on *dibothriocephalus* anæmia (1894),<sup>2</sup>

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in which he reports cases of extreme anæmia with red cells of an average diameter bordering on  $9.0\mu$ .

It is not altogether irrelevant to remember that in these three diseases, which have similar blood pictures, there is much in common clinically. In each gastro-intestinal symptoms are a feature, and glossitis, which is a familiar symptom in sprue and Addison's anæmia, is reported by Becker<sup>3</sup> to occur frequently in *dibothriocephalus* infection, although Schauman states that he has never observed it.

The suggestion arises that there is a common factor at work.

### METHODS

The blood-films were in each case collected at approximately the same time—about noon. They were fixed and stained with Leishman's stain. Measurements of the cells were made by projecting the image by means of a Zeiss microphotographic apparatus on to a white surface and measuring the image as described in a preceding communication (1924).<sup>5</sup>

### APPENDIX

#### *Protocols of cases recorded above*

The three cases of experimental infection with *Dibothriocephalus latus* R.L., B. and M., were infected on September 22, 23, and October 4, 1922, respectively, by swallowing the plerocercoid stage of the parasite. Treatment and evacuation of the fully developed *Dibothriocephalus latus* were carried out on January 7, January 6, and July 2, 1923, respectively. The numbers of the worms which developed in each case were three in R.L., three in B., and one in M. The full history and progress of each case will be embodied in a detailed account of the experiment, which is to be published shortly by Professor Leiper, who has kindly provided the material which has formed the basis of this publication.

The Esthonian Seaman, C. E., age 32 years, left Riga, January 12th, 1924.

Jan. 15th. Sudden onset of diarrhoea.

Jan. 19th. Arrived in Aberdeen. Admitted to City Hospital; stools typically dysenteric—blood and mucus.

Jan. 20th. Anti-dysenteric serum given.

Jan. 21st. Much improved. Temperature normal—highest previously  $99^{\circ}$ .

Jan. 26th. Allowed up and discharged on 27th.



Fæces not found to contain dysentery bacilli or amœbæ. Ova of *Dibothriocephalus latus* were numerous at all examinations. No agglutination of *B. dysenteriae v.w.x.y.z.* or Shiga was obtained with patient's serum.

Feb. 4th. Readmitted with Temp. 104°. Blood culture *B. typhosus*. Widal positive (*B. Typhosus*).

Feb. 9th. Three tapeworms passed. Blood Count: Reds, 4,960,000; whites, 5,500 per cub. mm. Hæmoglobin, 79 per cent.

Mar. 18th. No ova in his fæces. Patient had had a moderately severe attack of typhoid fever. Reds, 4,600,000; whites, 6,200 per cub. mm. Hæmoglobin 82 per cent.

These data were kindly supplied by Dr. Smith, Pathologist to the City Hospital, Aberdeen.

#### CLINICAL NOTES OF SPRUE CASES (Dr. G. Low)

(1) *Case H.*—Age 40. Penang, 1910, for 9 months. Malay States, 1916–1919. Penang, 1921–1922.

*Previous illnesses.*—Chicken pox and whooping-cough. No specific disease.

*Landed U.K.* Oct. 1922.

*Admitted Hospital*, 8.1.24.

*Symptoms.*—Sallow complexion; white formed stools, flatulence. Case of chronic sprue. First symptoms in 1919, diagnosed sprue 1921.

Relapses, 1921; 1922, one month after returning to England. Progress slow, relapse after leaving hospital.

(2) *Case L.*—Age 42. India, 1914–1923.

*Previous illnesses.*—Dysentery 1915. No specific.

*Present illness.*—Symptoms of sprue, April 1923. Loss of weight, diarrhœa, sore tongue, etc.

*U.K.* May 18th, 1923.

*Admitted to Hospital*, January 1924. Much emaciated. Typical case of sprue.

(3) *Case A.*—Aged 60. India.

*Previous illnesses.*—Dysentery, hepatitis, threatening liver abscess 1903, and again in 1904. Malaria frequently. Cholera 1917. Ptomaine poisoning. Syphilis, years ago.

Sprue began 1920 and has continued since. Has had periods of treatment in 1922, 1923 and 1924. Typical case of sprue, but complicated by the specific infection.

(4) *Case B.*—Age 40. China, East Indies, 1901–1906, Mediterranean 1908–1910, China 1919–1922.

*Previous illnesses.*—None of note.

*Present illness.*—Sprue began August 1921. Diarrhœa, loss of weight, sore tongue, pain in left side abdomen, etc.

*Admitted to Hospital*, 2.11.23. Thin, typical case of sprue. Now, 3.4.24, practically well again after treatment.

(5) *Case F.*—Age 44. India and Ceylon since 1910.

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*Previous illness.*—Malaria off and on. 1917 enteric, no complications. 1922 pyorrhœa, teeth removed.

*Present illness* began March 1923, diarrhœa with light stools, sore mouth, typical sprue. Spleen one finger below costal margin.

*Landed U.K.* 14.1.24.

*Admitted Hospital,* 15.1.24. Clear case of sprue, typical in every way.

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## GASTRIC SECRETION, PHYSIQUE AND PHYSICAL FITNESS

By M. McC. BAIRD, B.A., J. M. H. CAMPBELL, D.M., Beit Memorial Research Fellow,\* and J. R. B. HERN, B.A. (From the Department of Physiology, Guy's Hospital.)

DUODENAL ulcer occurs more frequently in the man of good or at any rate of average physique, and gastric ulcer more frequently in the woman of poor physique. Duodenal ulcer is frequently associated—it may be as cause or effect—with a hypertonic and hyperchlorhydric stomach. The idea of a diathesis predisposing to each disease has assumed very different prominence at different periods of medical history. Recently it has been emphasised by Hurst,<sup>3</sup> Dauwe,<sup>4</sup> and others in the case of gastric and duodenal ulcers, which they have suggested are often family diseases with different types of stomach as the underlying diathesis.

Arguing from this it seemed likely that there might be in health some relationship between the amount of acid in the gastric secretion and the tone and position of the stomach, and the physical fitness and build of the subject.

The investigations resolved themselves into attempts to answer three questions. Is it possible to grade men by the various tests which have been proposed to measure physical fitness? How far does the amount of acid in the gastric juice depend on the fitness and general build of the subject? And what relation is there between the rate of emptying and the acidity of the stomach as judged by the test meal, and its rate of emptying and tone and position as judged by x-rays; and how far can the position of the stomach be correlated with muscular development or with any anatomical measurements which represent however imperfectly the inherited constitution or diathesis of the subject?

The first question will only be referred to shortly here as it has been dealt with as part of a general report to the Medical Research Council.<sup>18</sup> As no single test was found to give good agreement with the physical fitness of the subjects as judged by men who knew them well, this general grouping has been made use of here in preference to the result of the tests. The second and third questions are answered as far as possible in this and the following papers; other points which have arisen and

\* The experimental part of this work was done during the tenure of the Hilda and Ronald Poulton Fellowship at Guy's Hospital.

some experiments with the duodenal tube have already been described in this journal.<sup>17</sup>

#### CLINICAL ANTHROPOMETRY

Before describing the methods of investigation which were adopted, one or two other points will be referred to. After most of this paper was written a preliminary account with the above title was published from the Presbyterian Hospital, New York.<sup>16</sup>

The idea of the authors was somewhat similar to our own, to obtain some measurements of the physical types specially prone to develop certain diseases, but naturally the details chosen for investigation were entirely different. Their complete scheme involved measurements which were classified as anatomical, physiological, psychological and immunological, but the preliminary account only deals with four anatomical measurements in 50 subjects with disease of the gall bladder and 39 subjects with gastric or duodenal ulcer. In each case the diagnosis was confirmed by operation.

Even in this limited field some surprising correlations were found. The points specially considered were the relation of weight to height, the angle formed by the costal margins, the angle of the ascending and horizontal rami of the mandible, the depth of the jaw anteriorly and posteriorly and the depth of the chest. In the subjects with disease of the gall bladder the weight relative to the height was greater, the costal angle was wider and the depth of the chest was greater. Perhaps these results are not very surprising, but it is curious to find that in the same group the upper jaw was wider and squarer and the angle between the ascending and horizontal rami of the mandible was nearer a right angle, while it was a more obtuse angle in the subjects with ulcer.

Of course in both groups there was a great deal of overlapping with normal subjects, and in some of the points considered there was some overlapping between the two groups of diseases, but the surprising thing is that there was any real distinction, and the authors state that in these subjects with definite abdominal disease, these five measurements led to the right differential diagnosis nine times out of ten. It is unlikely that such methods will ever become of much importance in the diagnosis of an individual case. Probably they help to explain the success of the experienced physician who may make use of such measurements unconsciously, and ultimately they may make it easier for him to hand on his experience to others.

Some years ago Friedman drew attention to quite a different distinction between gastric and duodenal ulcers.<sup>1</sup> If cases with hæmatemesis or visible melæna were excluded, he found that anæmia was more common in gastric ulcer, and that in duodenal ulcer there was actually a tendency to polycythæmia. He examined 50 consecutive patients in all of whom the diagnosis was confirmed at operation. In the cases of gastric ulcer the hæmoglobin percentage averaged 75 and varied from 55–110, while in the cases of duodenal ulcer it averaged 90 and varied from 65–120.

Further observations on this subject are required, but some observations of Nesor<sup>10</sup> suggest a possible explanation. He found that when a horse was exercised vigorously and regularly the hæmoglobin percentage was increased enormously. In three young race-horses the red cell count rose from 6·5 to 8·6, from 6·9 to 8·1 and from 7·0 to 9·0 millions per cub. mm. In a large series of horses of all types he found that the corpuscular volume rose from 28 per cent. in stalled horses to 33 in partially stalled horses, to 40 in fast working horses and to 46 per cent. in trained racing horses.

Brown has shown experimentally in dogs that exercise is an effective stimulus to the bone marrow.<sup>12</sup> It may be that the relative tendency to polycythæmia in duodenal ulcer found by Friedman merely means that duodenal ulcer is more likely to occur in men who are taking exercise, and gastric ulcer in men who are leading a sedentary life. This will be further considered later.

#### METHOD OF EXAMINATION

The routine proposed was to carry out a series of tests for physical fitness on normal students, and to compare the grading by these tests with the grading arrived at more directly by the man's physique and athletic performances. This grouping was done by various teachers and fellow-students who knew the men well, but knew nothing about the result of the tests.

The same men were to be examined with x-rays after an opaque meal, and their gastric secretion examined by a fractional test meal as suggested by Rehfuss,<sup>2</sup> following exactly the technique described by Bennett and Ryle.<sup>5</sup> Originally certain other tests were included in the scheme, such as for sugar tolerance, for urea concentration, for fatigue and some psychological tests.

It has not been possible to carry out this scheme entirely, but 80 students of this hospital were examined by various tests for physical fitness; 30 of these and 31 others (including four

women students of another hospital) volunteered for the test meal, and most of these were also examined by x-rays. These three investigations have been carried out previously, but not at the same time and on the same men.

We wish to thank very heartily the large numbers who offered themselves for these, sometimes rather unpleasant, proceedings. The volunteers were medical students, and except that two or three men were excluded because of a history of indigestion, they were not selected in any way.

#### GROUPING OF GASTRIC ACIDITY

The wide variations in the gastric acidity which may occur in healthy subjects are now generally accepted, but in a recent review <sup>11</sup> no suggestion is made that these variations depend on any particular factor, such as build or physical fitness.

To compare the physical fitness and gastric secretion, the amount of acid in the stomach has to be classified in some way, although such a course must be quite arbitrary. Many curves fall just on the border line and might easily be placed in either of the two groups. To avoid any undue bias the grouping was made at an early stage before any other results had been considered and was strictly adhered to.

The following classification proposed by Bell <sup>9</sup> has been used because it was easy to apply. Group 1. Achlorhydria, in which free acid as indicated by di-methyl is absent throughout. 2. Hypochlorhydria, in which the curve of free acid has not exceeded the 10-unit line (0.086 per cent. HCl). 3. Low Normal, 4. Normal, and 5. High Normal, in which the curve of free acid has not exceeded the 20-, 40- and 50-unit line respectively. These three groups include the same curves as the lower middle and higher parts of the area found by Bennett and Ryle <sup>5</sup> to contain 80 per cent. of normal students. 6. Hyperchlorhydria, in which the curve of free acid has exceeded the 50-unit line (0.18 per cent. HCl). One slight modification has been made, *i.e.* these subjects where the curve only just crossed the line on one occasion have been put in the lower group.

The distribution of the students among the various groups is given in Table I, where the results of Bennett and Ryle <sup>5</sup> are included for comparison. Only four women were examined, and as two of these fell into groups which were unusual among the men and as the same thing was found at their x-ray examination probably quite different standards of normality are needed for women. For these reasons and because they

were not graded or given the tests for physical fitness the women are not further considered in this paper.

TABLE I.

Number of students (as percentage) in each of these six groups according to the maximum percentage of HCl found in the curve for free acidity.

	Number of subjects.	1. Achlor-hydrria.	2. Hypo-chlor-hydrria.	3. Low Normal.	4. Normal.	5. High Normal.	6. Hyper-chlor-hydrria.
This series . . . .	57	2	7	26	41	14	10
Bennett and Ryle .	100	4	1	10	59	18	8
Combined . . . .	157	3	3	15	53	17	9

Over 80 per cent. of the subjects fell into the three middle groups. As the other groups, 1, 2 and 3, are found much more frequently in various diseased conditions, and as curves of these groups are often taken as evidence of disease it is important to examine the men who fell into these groups and see if they can really be regarded as normal in every way.

#### PHYSICAL FITNESS AND GASTRIC ACIDITY

Six men fell into the hyperchlorhydria group and five into the achlorhydria or hypochlorhydria groups. All these men were given the various tests for physical fitness, but as there was considerable divergence between the results of the different tests and their significance is uncertain, the grouping which was arrived at by a large number of independent observers has been used. The men were divided into four groups, (A) athletes, (B 1) men above the average, (B 2) average, and (C) below the average. The result is shown in Table II.

TABLE II.

Physical fitness of subjects with unusual test-meal findings.

Test-meal findings.	Athletes (A).	Above the average (B1).	Average (B2).	Below the average (C).
6. Hyperchlorhydria.	{ 86 * 104	25 26	50 98	
1 and 2. Hypo- and A-chlor-hydrria.	{		84 87 106	62 85

As average in these tests was used to include a rather low standard, *e. g.* men who were not playing games regularly,

\* These same serial numbers for the subjects are used in these two papers and in the report on the tests for Physical Fitness <sup>18</sup> to facilitate references and to save repetition. Numbers 62, 84 and 85 have been fully discussed in our previous paper, where they were referred to as A, B and C, respectively.

these results support the view that hyperchlorhydria is more common among athletes and men taking regular vigorous exercise, and hypochlorhydria more common among those leading a more sedentary life.

Admittedly there are only a small number of results from which to draw conclusions, even when all the subjects are tabulated according to the amount of acid in the gastric juice and their state of physical fitness. The results are shown in Table III.

TABLE III.  
Relationship of physical fitness and gastric acidity after the test meal.

Group.	1. Achlorhydria and 2. Hypochlorhydria.	3. Low normal, 4. Normal, and 5. High normal.	6. Hyperchlor- hydria.
Athletes (A).	0	10	2
Above average (B1) and Average (B2).	3	29	4
Below average (C).	2	7	0

No men who were classified as athletes have hypo- or achlorhydria, and no men classed as unfit have hyperchlorhydria. Most cases of hypochlorhydria occur among men who are taking no regular exercise.

But if smaller variations from the normal are considered, *i. e.* high and low normal, there is no evidence that this degree of acidity of the test-meal curve is influenced by the fitness of the subjects. It is true that no unfit men ever show a high normal curve, but among the athletes there are a large number of low normal curves. Within the limits covered by the three middle groups the differences depend on individual characteristics rather than physical fitness, but outside these limits hyperchlorhydria is more often associated with an active life and hypochlorhydria with a sedentary life.

#### GASTRIC ACIDITY AND PHYSIQUE

The association between the position of the stomach and the shape of the chest has been recognised for some time. In the following paper this is considered in more detail, and the ratio of the circumference of the chest to the stem length is shown to give a good indication of the position of the stomach. A definite association is also shown between the results of the x-ray and chemical examination of the stomach.

As the stomach which is high in position and empties rapidly after a barium meal occurs most frequently with a short broad



chest, and as from another point of view it occurs most frequently with hyperchlorhydria, it seemed possible that there might actually be some association between the shape of the chest and the acidity of the stomach. Table IV shows that this

TABLE IV.

Showing the association between the acidity of the stomach and the shape of the chest.

Men with hyperchlorhydria.				Men with hypochlorhydria.			
Number of subject.	Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length	Number of subject.	Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length
25	93	89	1.04	62	85	95	0.89
26	97	86	1.12	84	86	95	0.90
50	84	87	0.96	85	83	89	0.93
86	92	88	1.04	87	77	86	0.89
98	87	92	0.95	106	92	90	1.02
104	93	91	1.02				
Average	91	89	1.02	Average	84	91	0.93

is so, and that hyperchlorhydria occurs more frequently in the man with a relatively short broad chest and hypochlorhydria more frequently in the man with a relatively long narrow chest. The association is not as close or as constant as between the position of the stomach and the shape of the chest, but it is quite definite.

As the acidity of the stomach is correlated with the shape of the chest and also with physical fitness, some relationship might be expected between physical fitness and the shape of the chest. Hyperchlorhydria occurs most frequently in men playing games regularly and never in men who were classed as below the average. It is also associated with the relatively short broad chest. This suggests that the relatively short broad chest will be more common among the athletes.

Comparing the relative chest and stem length measurements in the 80 students examined there was some truth in this, but no very great difference. In the athletes the average circumference of the chest was 91.5 cms. for a stem length of 90.9 cms., while in the men who were grouped as "average" and were not playing games regularly the chest averaged 87.7 cms. for a stem length of 90.3. There was less difference between these groups than between the men with hyper- and hypo-chlorhydria, and there were of course many exceptions among both athletes and average men.

We do not mean to imply that the tall thin man may not be a successful athlete, but merely that when the men were considered for physical fitness hypochlorhydria and lack of

regular exercise were found to be associated, and when the men were considered for the shape of their trunk, hypochlorhydria and a relatively long narrow chest were associated.

#### RATE OF EMPTYING

This was found to be very variable, as in Bennett and Ryle's series. The comparative results are shown in Table V. Except in Number 50, who apparently emptied in less than a quarter of an hour the first time and a more normal result two days later,

TABLE V.

Rate of emptying of the gruel meal. Figures given as percentages.

	Average time of emptying.	Stomach contains no starch at							
		1 hr. or be- fore.	1½ hrs.	1¾ hrs.	1½ hrs.	2 hrs.	2½ hrs.	2¾ hrs. or later.	
This series (57 men) . .	2.1	5	7	14	9	17	16	10	22
Bennett and Ryle (100 men) . . . . .	1.9	6	3	7	13	17	14	18	22
Combined (157 men) . .	2.0	5.5	4	9.5	12	17	15	15	22

the stomach was never empty at three-quarters of an hour and only three times at one hour. The average time was just over two hours, and the usual time was between 1½ and 2½ hours, but one man was not empty till four hours.

Of the three men whose stomach was empty in an hour, two (numbers 87 \* and 106) were grouped as hypochlorhydric and one (63) as low normal. Of the four at 1½ hours, one (62) was achlorhydric on three occasions, one (84) was hypochlorhydric and the other two (12 and 91) were low normal.

The eight whose stomachs were empty at 1¾ hours formed a much more heterogeneous group. One (85) was hypochlorhydric, so that one of the very few constant findings was that all the five stomachs with achlorhydria or hypochlorhydria emptied at or before 1½ hours. One (50) was actually hyperchlorhydric. The others were near to the normal, three being low normal and three being just above the average in spite of their rapid emptying. The average maximum acidity for these eight men was practically the average for the whole series, but the average for the seven emptying at or before 1¾ hours was very much below normal.

At the other extreme there were eleven men with food in the stomach at 2½ hours. Six of these were so nearly empty that

\* These same serial numbers are used in this and the following paper and in the report to the Medical Research Council in the tests for Physical Fitness.<sup>18</sup>

they need not be further considered, especially as they were normal in other ways. Four of the remaining five were fairly similar, a large amount of starch still being present at  $2\frac{1}{2}$  hours. In two (82 and 86) the meal was not continued further, and in two (26 and 101) starch was absent at 3 hours. As regards acidity 101 was normal, 82 was low normal and 26 and 86 were both hyperchlorhydric.

The latter was one of the two subjects who really disliked the whole proceeding, and said that he was ill for two days after. The only other who was upset was 98. He developed a headache soon after swallowing the tube, and this continued. After two hours he vomited up the tube and much of the meal, and even then did not feel well enough to have any lunch. This may have been an example of a reflex gastric headache. All the others felt quite comfortable as soon as the meal was over, and were able to eat a good lunch, even if they had not been very happy during the course of the experiment. Incidentally only one man (77) who came for the test meal went away without being able to swallow the tube.

In the other subject (78) whose stomach emptied slowly, a large amount of starch was present after  $3\frac{1}{2}$  hours, and it was not absent till after four hours. His acidity was high normal. It seems most likely that this delay was due to the conditions of the experiment rather than the normal state of affairs for his stomach. He came with 77, and was possibly influenced by his failure. 78 was the only failure with the x-ray examination, as he vomited after the barium meal.

There is not very much in common among these men whose stomachs emptied slowly, but the acidity of their curves was above the average, as there were two hyperchlorhydrics and one high normal. But three of the hyperchlorhydrics (25, 98 and 104) emptied in the usual time of 2 hours, and one already referred to emptied more rapidly than usual, so that no general rule can be made here.

These results may be summarised as follows :—

(1) Men whose stomachs emptied at or before  $1\frac{1}{4}$  hours all have a low acidity.

(2) Men whose stomachs emptied at  $1\frac{1}{2}$  to  $2\frac{1}{2}$  hours (inclusive) have average acidity, and within these limits there is no further association between lower acidity and more rapid emptying.

(3) Men whose stomachs emptied after  $2\frac{1}{2}$  hours may have normal or high normal acidity or hyperchlorhydria, but there is a higher proportion of the latter.

(4) In all achlorhydrics and hypochlorhydrics examined the stomach was empty at  $1\frac{1}{2}$  hours or before.

(5) In the hyperchlorhydries the stomach may empty rapidly, normally or slowly, but slow emptying occurs in a high proportion.

#### THE OPENING OF THE PYLORUS

In a recent paper <sup>17</sup> various reasons were given for thinking that the degree of relaxation of the pyloric sphincter is under reflex control, acid on the gastric or duodenal side being only one of the factors which may influence it. Since then Carlson <sup>14</sup> has reviewed a large amount of evidence and brought forward fresh evidence of his own which shows this much more conclusively. His method of investigation was recording peristalsis and time with a balloon in the pyloric canal.

His main conclusions were as follows. Both motor and inhibitory effects may be obtained by stimulation of the vagus and sympathetic. Appropriate stimuli of all sensory visceral nerves and some somatic sensory nerves may increase the contraction of the pylorus. The vagus is not necessary for this. Various chemical and mechanical stimuli of the duodenal mucosa may be equally effective. Alkali may have the same result as acid, so it is certainly not correct to speak of the "acid control" of the pylorus. The same stimuli on the gastric side of the pylorus are without any constant effect on its time. He suggests that in duodenal ulcer it is over-excitation or hyper-excitability of the nervous reflex rather than the increased acidity which prevents the normal relaxation of the pyloric sphincter.

Nakanishi <sup>15</sup> has shown that in the rat the *main* effect of the vagus is inhibitory to the pyloric sphincter, and the *main* effect of the sympathetic is increased contraction, but that the opposite effects may also be obtained.

#### RESTING JUICE

This seemed worth examining carefully, because if any reliable conclusions could be drawn from it, time and trouble would be saved in the subsequent test meal. The average amount of resting juice was 50 c.c. It varied from a few c.c. to 145 c.c., and was over 100 c.c. in one-tenth of the cases. Bennett and Ryle say that where the resting juice is large in amount there are usually higher figures for the free acid both in the resting juice and in the subsequent curve.<sup>5</sup> This is not borne out by our figures.

Of the 17 cases where it was 60 c.c. or more, in the great majority the curve of acidity was normal. It is true that it was above normal four times, but twice it was below normal.

Nor is the acidity of the resting juice itself high, for in eight of these there was no free HCl, and in the other nine the acidity was within the normal limits. It might be that this apparent low acidity is due to dilution with saliva or bile, but in two cases there was a copious resting juice of low acidity without any bile.

In view of the supposed connection between hyperchlorhydria and hyper-secretion this question was approached in another way. In the seven cases of hyperchlorhydria the average amount of resting juice was 45 c.c., just below the average figure, and for the six cases of achlorhydria and hypochlorhydria it was 33 c.c. As one of these six had 110 c.c. resting juice the average was under 20 c.c. in the other, although three of them were bile-stained. This suggests that the hypochlorhydric stomach really is deficient in the amount of its secretion, but the opposite does not seem to hold true. Probably the amount of resting juice is not of much importance as it is a product of so many different conditions.

The acidity of the resting juice varied considerably and the average value was low. In nearly two-thirds of the subjects there was little if any free acid and about 10 parts total acid. Most of the others were considerably above the average, and this included five of the seven hyperchlorhydrics. Thus high acid in the resting juice makes hyperchlorhydria more probable, but low acidity or a small quantity of resting juice does not exclude hyperchlorhydria.

No close connection could be shown between the acidity of the resting juice and the height to which the acid curve subsequently rose, or between the acidity of the resting juice and the rate of emptying.

#### BILE IN THE RESTING JUICE AND LATER FRACTIONS

In about one-third of these subjects the resting juice was deeply bile-stained from the beginning; in about half bile was absent, and in the rest the juice was only slightly bile-stained, or was clear at first and became bile-stained later. It is difficult to know if bile is present in the resting stomach normally or appears as the result of the nausea and retching. Its frequent appearance later in the meal without nausea suggests that it is quite a normal occurrence. Where the resting juice was above the average, *i. e.* 60 c.c. or more, bile was present in more than three-quarters of the cases, but it was sometimes present where the resting juice was very small in amount.

The only definite conclusion is that bile is rather more frequently present in the resting juice in the cases of hyperchlorhydria. This is shown in Table VI.

TABLE VI.

Presence of Bile in the Stomach (figures percentages).

	Number of cases.	Bile in resting juice.	Bile in course of the meal.	Bile absent from both.	Bile present in both.
Hyperchlorhydria 6	6	70	60	14	44
High normal 5, Normal 4, and Low normal 3	46	52	44	31	27
Achlorhydria 1, and Hypochlorhydria 2	5	50	33	33	16

Taking the resting juice of the cases as a whole bile was present in more than half, and it returns at some time during the course of the meal in nearly half, and most commonly about  $1\frac{1}{2}$  or  $1\frac{3}{4}$  hours. Sometimes it returns just after the peak of the curve has been passed, but more frequently just after the stomach is empty.

It occurs least commonly in the curves which are "climbing" in shape, and this would suggest that absence of regurgitation of bile is a cause of hyperchlorhydria, but Table VI shows quite clearly that this is not so, for it is present more frequently in the resting juice and in the course of the meal in hyperchlorhydrics than in any other group. Probably it is one of the mechanisms for preventing too great a rise in acidity.

Although a free regurgitation of bile is a possible cause of low acidity there is little evidence that this is so, for it is least commonly present in the cases of achlorhydria, hypochlorhydria and even low normals. The more acid the gastric contents the more likely is bile to appear during the course of the meal. Bile in the stomach is not the cause of low acidity, nor is the absence of bile the cause of high acidity.

#### VALIDITY OF THE FRACTIONAL TEST MEAL

Something must be said about the reliability of the fractional method, as it has been widely criticised. Gorham<sup>6</sup> gave the usual test meal and after an hour aspirated the stomach with a 10 c.c. syringe till it was empty and titrated the specimens separately. He found wide variations, and concluded that the stomach contents were not sufficiently well mixed to allow of a 10 c.c. specimen being taken as representative. There is some truth in this.

Often two specimens of different acidity and chloride content can be withdrawn by swallowing or pulling up the tube for two or three inches. Sometimes one specimen is colourless and the other bile-stained. Generally the change has not been very

great when the gruel meal has been used, but if the meal does not mix well it may be enormous.

In one pathological subject who had breakfast with eggs before coming for the gruel meal the stomach could not be fully emptied. As each specimen was withdrawn during the first hour it was possible to get two quite different samples by moving the tube a little. One was mainly the gruel meal and the acidity was low (about 0.04 per cent. HCl) and the other was the residue of the earlier meal, mainly fat and egg, with an acidity of 0.25 per cent. HCl. At 2½ hours the whole stomach contents were withdrawn by Gorham's method and mixing was then found to be fairly complete. In the ordinary routine with the gruel meal we have never found large differences like this.

This question has also been studied by Wheelon.<sup>7</sup> With the same subjects on different days he examined the gastric function by the ordinary fractional method, by withdrawing the whole meal together at one hour and by Gorham's method. He confirmed the differences in various parts of the stomach at the same time, but did not find that they were enormous. For example, in three typical subjects examined consecutively, from each of whom ten specimens were withdrawn, the classification of the acidity would have been as follows:—

- (a) Low normal in 9, hypochlorhydria in 1.
- (b) Normal in 6, high normal in 8, hyperchlorhydria in 1.
- (c) High normal in 1, normal in 8, low normal in 1.

With the exception of one specimen in (b) the changes are not very great, and they only emphasise that the test meal is giving a rough idea of what is taking place and not an absolutely accurate measure. For many purposes this may be sufficient. Wheelon's general view was that changes in different parts of the stomach are important, but not sufficiently great to invalidate the fractional method. Kopeloff<sup>8</sup> came to similar conclusions.

There are other reasons for thinking that the method is reliable. In the great majority of cases the curves of acidity conform to a definite type, rising fairly regularly to a maximum and then falling partly or completely.

In certain pathological states, *e. g.* pyloric stenosis due to ulcer, a certain type of curve is constantly found, and in other conditions some particular type of curve is generally found.

Finally, and most important, if the meal is repeated on the same subject the same sort of result, though not exactly the same result, is generally obtained. In a previous paper<sup>17</sup> were published three results on M.B. and four on F.J.M. at long intervals of time. All the curves conformed to the same type.

Bell and MacAdam have examined the same subject on 20 consecutive days, excluding Sundays, by the fractional method.<sup>13</sup> Again there are considerable variations in the actual figures, but the curves conform to type. According to the scheme which has been used here twelve of the curves would have been grouped as hyperchlorhydric, five as high normal, and three as normal. No doubt similar variations would have been found among these subjects, and some men who were classed as hyperchlorhydric would have been changed to high normal, and some low normals to hypochlorhydric, but probably there would have been no changes greater than these.

On the whole these considerations and the conclusions of other workers show that the fractional method gives a fairly accurate picture of what is taking place in the stomach, but that mixing is not always complete and may sometimes be very imperfect. Therefore small variations in the curve are not of any significance, and only its general shape and height should be considered. Dr. Hurst allows us to state that he has come to similar conclusions as a result of repeating test meals on a large number of patients. But if achlorhydria is found, it should always be repeated before assuming it is correct; occasionally but not often, it is not constant. If hyperchlorhydria is expected and not found, it is worth repeating the examination, as it is sometimes found on the second occasion.

#### SUMMARY AND CONCLUSIONS

1. The general results of Bennett and Ryle on the rate of emptying of the stomach and the range of acidity of the gastric juice after a gruel meal are confirmed in a further series of students.

2. Within certain limits (here grouped as normal or high or low normal) there is no association between the degree of acidity, the rate of emptying, and the physical fitness of the subject.

3. Outside this range hypochlorhydria or achlorhydria is more likely to occur in the man who is leading a sedentary life and is grouped as below the average as regards fitness. Hypochlorhydria only occurs in stomachs which empty rapidly.

4. Hyperchlorhydria is more likely to occur in the man who is leading a more active life. It may sometimes be associated with rapid or normal emptying, but more commonly with delayed emptying.

5. Hyperchlorhydria occurs more often in the man with a relatively short broad chest, and hypochlorhydria more often in the man with a relatively long narrow chest.



6. These results and the similar findings about the position of the stomach and the shape of the chest described in detail in the subsequent paper, provide some basis for a diathesis specially prone to develop certain gastric disorders.

7. Some evidence of the same nature from the Presbyterian Hospital, New York, is shortly described.

8. Bile probably occurs normally in the stomach—more frequently in subjects with higher gastric acidity—so that its function is partly at any rate to reduce too high acidity.

9. Further evidence has been brought forward by Carlson, confirming the view put forward in a previous paper, that the relaxation of the pyloric sphincter is under reflex control; and that the acidity of the gastric or duodenal contents is only one of the factors influencing this reflex, which can be acted on from very different sources, both through the vagus and through the sympathetic.

10. Various reasons are given for supposing that the fractional test meal does give a true idea of the course of digestion in the stomach, provided certain limitations about its accuracy are recognised.

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## COMPARISON OF THE TEST MEAL AND X-RAY EXAMINATION OF THE STOMACH IN HEALTH

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IN this examination of healthy students by various methods one object was to see if there was any constant association between the test meal and x-ray findings, *e. g.* if hyperchlorhydria generally occurred with a high hypertonic stomach in health, as so frequently happens in cases of duodenal ulcer.

Of the 61 students who had the test meal, 54 were examined with x-rays; 6 of the others were omitted for purely incidental reasons, and as their test meals gave normal results no special effort was made to examine them. The seventh (Number 78) would have been interesting to x-ray, as with the gruel meal he emptied more slowly than anyone else. Unfortunately he was sick twice after taking the barium meal and did not wish to try a third time.

### METHOD OF EXAMINATION

The following method was adopted as a routine, because it involved least disturbance of the man's ordinary work. Six ounces of barium sulphate were taken with water or cocoa at about 8 a.m., and afterwards each man ate as much as he liked of his usual breakfast. He worked in the dissecting room or elsewhere during the morning and was seen at midday.

The exact time between taking the barium and being x-rayed was not constant, but three or four men generally came together, and the man who had had breakfast first was examined first. A note was then made of the proportion of the barium which seemed to be left in the stomach and of the time since it was taken. Occasionally the stomach was empty or nearly empty, but in most men there was a large amount of food left after four hours, probably because breakfast had generally been taken as well as the pint of cocoa and barium.

This method, where varying amounts of breakfast were taken, is not a good routine method, and cannot give results which are comparable with other series, but reasons will be given later for thinking that the men marked as emptying most rapidly were not simply those who had eaten the smallest breakfast.

After this each man again drank six ounces of barium

\* The experimental part of this work was done during the tenure of the Hilda and Ronald Poulton Fellowship at Guy's Hospital.

sulphate, this time in a pint of water, and he was then examined for the tone and position of his stomach and for peristalsis. Notes were made at the time of these findings, and two drawings were made of the amount of food left from breakfast and of the position of the stomach, when the man was standing up after the second meal. The position of the stomach was judged by the level of the greater curvature above or below the iliac crests, when the subject was standing.

When all the men had been seen the notes and drawings were compared and each man was grouped in three ways, for the position and tone of the stomach and its rate of emptying.

The tone of the stomach is difficult to estimate with any accuracy, but this is not very important here, because there was only one man, normal in all other ways, where any special note was made of a difference of tone alone. In every other case the stomach was thought to be hypertonic where it was also high in position and rapidly emptying, and hypotonic where it was low in position and slowly emptying, and for this reason tone is not specifically referred to in the rest of this paper.

In this way each man was marked as having a stomach which was high, normal or low in position; and rapidly, normally, or slowly emptying. How far this method of judging the rate of emptying is accurate is open to dispute. The results agreed badly with the rate of emptying as judged by the test meal, but both these points will be discussed later. As already stated, it was judged mainly by the amount of food left in the stomach from the first meal, but the rate of emptying seen immediately after the second meal was also taken into account.

Certainly the position of the stomach is very variable in the same individual, and in several cases a note was made that a voluntary contraction of the abdominal muscles raised the stomach considerably. But the position which was drawn and made use of for classification was the position when the man stood up to be x-rayed without any special instructions on this point. It probably, therefore, represents the position with the usual tone of his abdominal muscles.

We wish to emphasise the fact that (with the exception of the four women) all the x-ray examinations, the notes and the final grouping of these were made by one of us (J. J. C.), who took no part in the test meals or the tests for physical fitness, and knew nothing about the results of these examinations. The grouping on the result of the test meals was done by one of us (J. M. H. C.) before he knew anything about the result of the x-ray examination. In this way the possibility of any unconscious bias was avoided.

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### UNUSUAL TEST-MEAL AND X-RAY RESULTS FOUND IN THE SAME MEN

Of the 54 (50 men and 4 women) who were x-rayed, 31 were passed as normal in every way, 15 differed from the normal in one, and 8 in both the points which were noted. Thirteen of these 54 were put in the unusual groups (hyper-, hypo- and achlorhydria) as the result of the test meal, and 41 were grouped as normal.

The most striking proof that these two methods really were picking out men who were unusual in some way, is that of the

TABLE I.

Showing that in most cases a subject who was picked out as unusual by x-rays was also unusual by his test meal.

	Percentage found as normal by test meal.	Percentage found unusual, i.e. in groups 1, 2 or 6.
Of 31 subjects normal by x-rays . . . . .	93	7
Of 15 subjects unusual in one particular by x-rays . . . . .	60	40
Of 8 subjects unusual in both particulars by x-rays . . . . .	38	62

8 who were picked out by one of us as the most unusual by x-rays, 5 were also picked out by the other as the most unusual by the test meal. And of the 18 found unusual by the test meal, 11 were unusual in at least one, and 5 were unusual in both of the points noted.

These findings are shown in Table I. Table II shows the x-ray and test-meal findings and some of the data of the tests for physical fitness in 25 subjects whose x-ray and test-meal findings differed from the "average" in some particular. Table III shows the same details for 29 subjects whose x-ray and test-meal findings did not differ from the "average" in any particular.

### THE POSITION OF THE STOMACH AND THE SHAPE OF THE CHEST. RESULTS OF OTHER WORKERS

It seems best to consider this first, because the position of the stomach was the most reliable part of the examination. Several workers had found some association between the position of the stomach and the shape of the chest, but we did not know that it was so close and do not think that this is generally appreciated. Faber<sup>3</sup> has recently reviewed the subject and has added some results of his own. In a large

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number of subjects he found that on the average the stomach is higher in men than in women, and lower in women who have borne children than in the others. The results are shown in Table IV.

Conran <sup>4</sup> has found a similar difference between men and women, but did not find an equally striking effect of pregnancy. Probably this was because he examined women with symptoms of dyspepsia, while Faber examined women in good health. Conran describes the subjects with low stomachs as having the

TABLE II.

Showing x-ray and test-meal findings and certain data of the tests for physical fitness in twenty-five subjects who differed from the "average" in some particular of their x-ray or test-meal examination.

Number of subject (1).	x-ray examination.		Test meal (4).	Physical fitness (5).	Measurements.		
	Position (2).	Rate of emptying (3).			Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length
86	+	+	6	A	92	88	1.04
94	+	+	5	B2	98	88	1.11
106	+	+	2	B2	92	90	1.02
21	+		4	B1	92	89	1.04
26	+		6	B1	97	86	1.12
38		+	4	B2	96	93	1.03
25		+	6	B1	93	89	1.04
104		+	6	A	93	91	1.02
52		+	3	B2	87	87	1.00
55		+	3	B2	96	87	1.10
101		+	4	B2	90	84	1.06
62		+	1	C	85	95	0.89
103		—	4	B2	82	91	0.90
85		—	2	C	83	89	0.93
107	—		4	B1	84	91	0.92
24	—		4	B1	86	92	0.93
49	—		4	B2	87	95	0.91
87	—		2	B2	77	86	0.89
37	—	—	4	B2	83	90	0.92
109	—	—	2	—	—	—	—
110	—	—	6	—	—	—	—
84	—	—	2	B2	86	95	0.90
63	—	—	3	C	90	97	0.93
98			6	B2	87	92	0.95
50			6	B2	84	87	0.96

(1) Numbers 1—80 were examined by all the tests for physical fitness. The others had not been examined in this way as a routine, but a few were done later where it was of special interest. 108—111 were women, all the others were men. These serial numbers are the same as in the previous paper.

(2) + high, — low. (3) + rapid, — slow. (4) 1, achlorhydria; 2, hypochlorhydria; 3, low normal; 4, normal; 5, high normal; 6, hyperchlorhydria. (5) A, athlete; B1, above the average; B2, average; C, below the average. (1), (2), (3), (4), (5), see Table II.

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TABLE III.

Showing x-ray and test-meal findings and certain data of the tests for physical fitness in twenty-nine subjects whose test-meal and x-ray findings did not differ from the "average" in any particular.

Number of subject. (1).	x-ray examina- tion (2) and (3).	Test meal (4).	Physical fitness (5).	Measurements.		
				Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length
1		5	A	99	92	1.08
3		4	A	95	97	0.98
5		3	A	80	89	0.90
7		3	A	88	88	1.00
11		3	A	93	90	1.03
23		5	B1	83	86	0.96
30		4	B1	86	88	0.98
39		3	B2	83	84	0.99
41		4	B2	90	89	1.01
51		3	B2	90	95	0.95
58		3	B2	91	94	0.97
59		4	B2	92	96	0.96
60		5	C	88	90	0.98
70		4	C	92	92	1.00
71		4	C	87	89	0.98
81		3	A	80	92	0.87
82		3	B1	—	—	—
83		4	A	—	—	—
88		3	C	—	—	—
90		4	B1	—	—	—
91		3	B2	—	—	—
93		4	B2	—	—	—
95		5	B2	—	—	—
99		3	B2	—	—	—
100		5	B1	—	—	—
102		4	A	—	—	—
105		5	B2	—	—	—
108		5	—	—	—	—
111		4	—	—	—	—

TABLE IV.

POSITION OF THE STOMACH IN MEN AND IN WOMEN WHO HAVE AND HAVE NOT BORNE CHILDREN (Faber).

Position of the stomach.	Percentages of subjects.		
	Men.	Women without children.	Women with children.
High, i.e. greater curvature above the umbilicus . . . . .	36	11	13
Average . . . . .	49	68	44
Low, i.e. lesser curvature below the umbilicus . . . . .	15	21	43

hypotonic diathesis and mentions that it may occur at a very early age. He does not give any special measurements of the shape of the chest, but describes the typical subject with a

low stomach as tall and thin, and considerably under weight in proportion to his height.

Faber points out the drawbacks of various measurements which have been proposed and himself makes use of the epigastric index. This is  $100a$  divided by  $b$ , where  $b$  is the distance from the umbilicus to the hollow between the end of the sternum and the ensiform cartilage, and  $a$  the width between the two costal margins half-way between the first two points. He finds that the greater the epigastric index—perhaps one can say the

TABLE V.

POSITION OF THE STOMACH IN 600 MEN AND WOMEN STUDENTS. (Moody, van Nuys and Chamberlain.)

Position of the greater curvature with reference to the iliac crests.	Percentage of subject (nearest whole figure).	
	Men.	Women.
More than 2 inches above . .	2	1
More than 1 inch above . .	5	2
Less than 1 inch above . .	18	10
Less than 1 inch below . .	23	19
More than 1 inch below . .	27	21
More than 2 inches below . .	16	22
More than 3 inches below . .	6	17
More than 4 inches below . .	3	8

broader the trunk—the higher is the stomach likely to be. Naturally there was much overlapping among individuals of the different groups, showing that many other factors were involved, and in women who had borne children the measurement was not of much value.

After this paper was written, Dr. Hurst drew our attention to some work by Moody, van Nuys and Chamberlain.<sup>5</sup> They made a complete x-ray examination and various other measurements in 600 healthy students—men and women. The position of the stomach was judged by the distance of the greater curvature of the stomach above or below the line joining the iliac crests, as in this series. The main measurements were the costal angle, the depth of the lumbar curve and the strength of the abdominal muscles.

They found that there were enormous variations in the position of the liver, of the stomach and of the colon; that the stomach was lower in women than in men, but that the liver was lower in men. The position of the stomach and colon was so low that, like everyone else who has worked at this subject, they deprecate the use of the terms gastropptosis and coloptosis with any pathological significance.

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Their findings as to the position of the stomach are shown in Table V. They have not drawn any very definite conclusions about the position of the stomach and the shape of the chest, but state that muscular development has little effect on the position of the stomach. In a few cases where they had the opportunity of making the observation, the gain or loss of 20 lbs. in weight did not make any difference to the position of the stomach.

### THE POSITION OF THE STOMACH AND THE SHAPE OF THE CHEST. RESULTS OF THIS SERIES

It seemed to us that a simpler and more direct measurement of the shape of the chest, or perhaps of the trunk, would be obtained by dividing the circumference of the chest by the length of the trunk. Both these measurements are easy to make and are in common use.

In the six men in whom the stomach was found to be highest by x-rays the chest measurement was 2 cms. or more greater than the stem lengths in every case. In the six men in whom the stomach was lowest the stem length was 6 cms. or more greater than the chest measurement in every case. In the next six highest and next six lowest there were individual exceptions, but the rule held for the majority. The fact that in the twelve most extreme cases there was no exception means that the shape of the chest, or rather of the trunk as a whole, is a most important factor in deciding the position of the stomach. The results for these twelve men are given in Table VI.

TABLE VI.

Showing the relatively broad chest where the stomach is high, and the relatively narrow chest where the stomach is low in position.

Stomach high by x-rays.				Stomach low by x-rays.			
Number of subject.	Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length	Number of subject.	Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length
21	92	89	1.04	24	86	92	0.93
26	97	86	1.12	37	83	90	0.92
38	96	93	1.03	49	87	95	0.91
86	92	88	1.04	63	90	97	0.93
94	98	88	1.11	84	86	95	0.90
106	92	90	1.02	87	77	86	0.89
Average	94.5	89.1	1.06	Average	85.0	92.3	0.92

We have no results for women to compare with these, but it is generally agreed that the stomach is more likely to be low in position in women than in men, even apart from child-birth. From Dreyer's tables <sup>1</sup> it is possible to get the average chest measurement for a man or woman of a given height, and



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as would be expected, the chest-stem length ratio is found to be much higher in men. These results are shown in Table VII.

TABLE VII.

Showing the chest to stem-lengths ratio in various groups.

	Chest (cms.).	Stem length (cms.).	Ratio of Chest Stem length
Six men in whom the stomach was highest	94.5	89.1	1.06
Average of seventeen athletes . . . . .	91.5	90.9	1.01
Average of all these cases (80) . . . . .	89.1	90.5	0.98
Dreyer's normal for man whose stem length is 90 cms. . . . .	86.0	90	0.96
Six men in whom the stomach was lowest .	85.0	92.3	0.92
Dreyer's normal for woman whose stem length is 90 cms. . . . .	77.9	90.0	0.87

The different proportions of the chest in men and women are evidently a factor in the different position of the stomach. As changes in the position seem to be associated with changes in acidity, it may be that this anatomical difference is one of the reasons why women are more likely to suffer from gastric and men from duodenal ulcer. Where the chest is relatively very broad or very narrow, this factor is the most important one in deciding the position of the stomach and overrules other factors such as the tone of the abdominal muscles.

Professor Pembrey suggested that the effect of the anatomical shape of the trunk, and therefore presumably of the abdominal cavity, influences the position of the stomach indirectly by its effect on the tone of the abdominal muscles. Other things being equal, the larger and narrower the abdominal cavity, the larger will be the span of the abdominal muscles between their insertions, and this will lead to decreased tone, and even, if the tone remains the same, to a greater tendency to give way and allow the stomach to drop.

### ASSOCIATION OF CHEMICAL AND X-RAY FINDINGS

The men who were unusual by one method of examination were frequently found to be unusual by the other as well. In no man with hyperchlorhydria was the stomach found to be low or slowly emptying, and in two-thirds it was actually found to be high or rapidly emptying.

The test-meal results which were grouped as normal and high and low normal are taken together because there were no great differences in these groups. Of these two-thirds were found to be normal by x-rays as well, and the variations might be in either direction.

Of the men with hypochlorhydria, the only constant finding

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was that they were never normal by x-rays. Three were, as expected, low or slowly emptying, but one was actually high and rapidly emptying. He seems to be an unusual type, but is certainly quite healthy, though not playing games regularly. The last of these five was Number 62, already referred to as unusual because he had achlorhydria on three occasions.

These results are shown in Table VIII and the details of individuals in Table II. In most cases hyperchlorhydria is associated with a high or rapidly emptying stomach. Hypo-

TABLE VIII.

Showing the x-ray findings in fifty men with hyper- or hypo-chlorhydria compared with the normal.

	Percentage found in when the stomach was		
	High or rapidly emptying.	Normal.	Low or slowly emptying.
Of six men with hyperchlorhydria (Group 6)	67	33	0
Of thirty-nine men in whom the stomach was normal (Groups 3, 4 and 5) . . . .	15	70	15
Of five men with hypochlorhydria (Groups 1 and 2) . . . . .	40	0	60

chlorhydria is found more often with a low and slowly emptying stomach, but it may occur with the reverse condition. If the rate of emptying is judged by the disappearance of starch after the gruel meal, hypochlorhydria is always found to be associated with a rapidly emptying stomach, so that here there is some conflicting evidence. This is discussed in a subsequent section.

### X-RAY FINDINGS AND PHYSICAL FITNESS

As there is some association between the physical fitness of the subject and the acidity of his gastric juice, and as the latter is related to the x-ray findings, there should be a relationship between these and the physical fitness. This is so, and in no one who was grouped as an athlete was there a low or slowly emptying stomach. And no one "below the average" had a high or rapidly emptying stomach, again excepting 62.

This may be due to the good tone of the abdominal muscles, perhaps associated with good tone of the visceral musculature as well. In view of the importance of the shape of the chest, the relatively broader chest of the athletes may be an important factor, but probably the tone of the abdominal muscles is of equal importance.

Such were our conclusions before reading the paper by Moody, van Nuys and Chamberlain <sup>5</sup> on 600 x-ray examinations

of healthy students. They say that muscular development was not a factor influencing the position of the stomach and that the stomach was not higher in athletes than in others. Their conclusions seem to rest much more on their test for the strength of the abdominal muscles than on general physical fitness. The tests consisted in the subject lying on his back and raising the trunk as frequently as possible. This certainly does not measure muscle tone, so much as the strength of the abdominal muscles and the endurance of fatigue. The strongest direct evidence in favour of our findings against their much larger series is the great change in the position of the stomach, which can be seen in so many cases when the tone of the abdominal muscles is increased by voluntary contraction.

#### THE RATE OF EMPTYING OF THE STOMACH AS JUDGED BY X-RAYS AND BY THE TEST MEAL

By the x-ray examination the stomachs of ten men were grouped as emptying more rapidly than normal, and of seven as emptying more slowly. The average time at which starch disappeared from the stomach in these two groups was just the same. Of the former only two emptied rapidly after the gruel meal as well, one of these having achlorhydria and the other hypochlorhydria. Two actually emptied slowly and the rest were average. The results were equally discordant with the group who emptied slowly by x-rays.

As already stated, the method of examination was not accurate because different quantities of food were eaten for breakfast. This was only allowed because the men who volunteered for the tests had already gone without breakfast for the test meal, and we thought that a second day without breakfast, especially when the men were doing an ordinary morning's work, would diminish the number of volunteers. The discrepancy in the rate of emptying after the barium meal and after the gruel meal might have been due to the different amount of breakfast taken with the barium, and the results would have been omitted all together were it not that the men who were found to empty slowly by the method formed a homogeneous group.

In each man whose stomach emptied slowly the chest measurement was less than the stem length, the average ratio being 0.92; while in each man except one whose stomach emptied rapidly, the chest measurement was greater than the stem length, the average ratio being 1.05. Again, the one exception was Number 62, and the rapid emptying of his stomach was due to achlorhydria. The figures are given in Table II.

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As the man with a short, broad chest has his stomach relatively high, and as the stomach of a man of this build tends to empty rapidly after a barium meal, it seemed likely that the rapid emptying might depend on the position of the stomach. In the seven men whose stomachs emptied slowly, five had stomachs which were grouped as low in position, and the actual distance of the greater curvature below the iliac crests was  $4\frac{1}{2}$ , 4,  $3\frac{1}{2}$ , 3, 2, 2 and 1 inches respectively. In the ten men whose stomachs emptied rapidly the greater curvature was on the average just above the iliac crests—being below in four (2, 1,  $\frac{1}{2}$  and  $\frac{1}{2}$  inches respectively), level in two, and above in four (2, 2,  $1\frac{1}{2}$  and 1 inches respectively).

Evidently after a heavy meal containing a large amount of barium the position of the stomach has some influence on the rate of emptying. Where the stomach is hypotonic the position of the stomach will appear lower when it is judged by the level of the greater curvature, so that the tone of the stomach is probably a factor as well as its position.

In view of this it seemed worth while examining the shape of the chest in the men whose stomachs emptied more quickly or more slowly than the average after the gruel meal.

Of the eight men whose stomachs were not empty after  $2\frac{1}{2}$  hours, three had a chest measurement much greater than their stem length and only one had the reverse. Of the thirteen men whose stomachs were empty at  $1\frac{1}{2}$  hours or before, only two had a chest measurement much greater than their stem length and six had the reverse.

In other words, the stomach tends to empty quickly after the gruel meal in the man with a relatively long, narrow chest, and in this same man the stomach tends to empty rather rapidly after the barium meal. Probably in the man of this build after the barium meal of considerable weight, mechanical factors such as the tone and position of the stomach are of the greatest importance in deciding the rate of emptying, while after the gruel meal these are of less importance, and the low hypotonic stomach is associated by hypochlorhydria and rapid emptying. With the more solid meal of everyday life the rate of emptying probably depends on both these factors.

It has generally been supposed that the rate of emptying was similar under all conditions, though it is well known that the average time after the gruel meal is about two hours, and after the usual barium meal about four hours. How has this view arisen? Bennett and Ryle<sup>2</sup> state, "the findings as to the rate of emptying made by x-ray observation of an opaque meal confirm the observations made by the gastric tube."

Dr. Ryle tells me that not very many subjects were examined from this point of view, and that the barium meal was made up much lighter than is usual, so that its average time of emptying was more nearly two hours, as with the gruel meal.

Many of the other data on which this opinion is based have been obtained from patients in bed, where the weight of the barium will not make so much difference. In many diseases the factors causing slow or rapid emptying may be powerful enough to be effective under all conditions. In the one subject in this series with achlorhydria there was rapid emptying after the gruel meal and after the barium meal.

In a subsequent series of test meals carried out at midday after an ordinary breakfast the power of the stomach to separate the different constituents of the food has been very noticeable. In several subjects a large proportion of the fat from breakfast has been in the stomach three or four hours after breakfast when the rest of the food has nearly or quite disappeared.

Evidently in healthy subjects where there is no pathological factor producing rapid or slow emptying under all conditions, the stomach behaves very differently with different meals. Possibly in some subjects the delay with the test meal is partly due to the presence of the tube and the resulting discomfort.

#### SUMMARY AND CONCLUSIONS

(1) The position of the stomach is mainly influenced by the shape of the trunk. Where the stomach is much above its usual position the circumference of the chest is at least 3 cms. greater than the stem length. Where the stomach is much below its usual position the circumference of the chest is at least 7 cms. less than the stem length in every subject examined. In intermediate positions the correlation is less definite, showing that other factors are involved.

(2) The relative position of the stomach in the men who were "below the average" and in the athletes suggests that the tone of the abdominal muscles is another important factor. The change in the position of the stomach when the tone of the abdominal muscles is increased by voluntary contraction supports this view.

On the other hand, Moody, van Nuys and Chamberlain concluded that muscular development was not a factor of much importance in deciding the position of the stomach, possibly because they used a method which measured the strength of the abdominal muscles rather than their tone.

(3) Everyone who has examined healthy subjects has found such enormous variations in the position of the stomach that

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the use of the same term gastropstosis, to indicate an anatomical position of the stomach compatible with perfect health, and the symptoms which are sometimes associated with it, is very undesirable.

(4) In health high acidity of the gastric juice is most commonly associated with a high hypertonic stomach which empties rapidly after a barium meal. It is found most frequently in men playing games regularly and in no subject in this series who was classed as "below the average." This group of findings is associated to some extent with a relatively short broad chest.

(5) On the other hand, low acidity of the gastric juice is generally but less constantly associated with a low hypotonic stomach, which empties slowly after a barium meal. It is found most frequently in men who were classed as "below the average" and in no subject in this series who was playing games regularly. This group of findings is associated to some extent with a relatively long narrow chest.

Among the exceptions is a subject with achlorhydria, whose stomach, as is usual in such cases, emptied rapidly after the gruel meal and the barium meal, and was normal in position.

(6) The conclusions about the rate of emptying are conflicting and require confirmation. Like all other observers, we have found that rapid emptying after the gruel meal and hypochlorhydria are closely associated.

The x-ray findings are different, and in each case slow emptying was found in a relatively long, narrow chest, generally with a low hypotonic stomach. It may be that with a heavy barium meal the mechanical factors such as the tone and position of the stomach are of primary importance, and that with the ordinary gruel meal other factors, such as peristalsis and especially the degree of relaxation of the pyloric sphincter, predominate.

(7) These results of the x-ray examination confirm the conclusion of the previous paper, that certain anatomical and physiological variations present in health may be the physical basis of the subjects' diathesis or tendency to develop certain gastric disorders under appropriate influences.

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## TWO CASES OF NEUROFIBROMA OF THE CERVICAL SYMPATHETIC

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*Case 1.*—F. K., aged 37, was admitted to hospital under Mr. Slesinger, with a swelling in the neck on the left side. He had noticed this for the first time about fifteen months previously; it was then about the size of a hazel-nut and caused him no pain or inconvenience. During the last twelve months the tumour had gradually become larger and had commenced to ache slightly. The patient could assign no cause for its appearance.

On admission there was a tumour on the left side of the neck, underneath the middle portion of the sterno-mastoid muscle. It was about the size of a hen's egg: the skin and sterno-mastoid muscle were freely movable over it. It seemed to be attached to the deeper structures: the carotid pulsation was transmitted to it, and it had fairly free mobility from side to side but not in an up or down direction. There were no other swellings in the neck, and no other abnormality could be found.

No diagnosis was made.

At operation, the tumour, which was exposed by splitting the sterno-mastoid muscle in the direction of its fibres, was found lying on the prevertebral fascia, just external to the bifurcation of the common carotid artery. Its upper and lower poles were attached to a structure which was running vertically; these attachments were divided and the tumour removed. After the operation the patient had well-marked enophthalmos, narrowing of the palpebral fissure, small pupil, and sweating changes on the left side.

Histological examination showed that the tumour was a neurofibroma without ganglion cells.

*Case 2.*—G. R., aged 32, had been aware of a tumour in the left side of his neck for two years. It had increased steadily in size during this time, but had given rise to no pain or inconvenience. As far as he knew, it had appeared spontaneously.

When admitted to hospital under Mr. Slesinger, he had a tumour about the size of a walnut in the left side of the neck. It was covered by the middle portion of the sterno-mastoid muscle, but projected slightly into the posterior triangle. The superficial structures were freely movable over it, and it had fairly free mobility from side to side but not in an up and down direction. It was smooth, of a fairly soft consistency and was not tender.

Neurofibroma of the cervical sympathetic was diagnosed.

At operation, the tumour, after exposure by splitting the sterno-mastoid muscle longitudinally, was found lying on the prevertebral fascia external to the carotid sheath. The capsule which covered it was incised and the tumour was shelled out. After the operation there were no signs of sympathetic paralysis.

Histological examination showed that the tumour was a neurofibroma without ganglion cells.

The evidence that these were tumours of the cervical sympathetic is clinical in the first case, and anatomical in the second case.

In the first case, from the symptom complex after the operation, it seems certain that the sympathetic was cut, and since the only definite attachments of the tumour were to a cord

running vertically in the neck, which was cut at its attachments to the upper and lower poles of the tumour, it seems that it was definitely a neurofibroma of the cervical sympathetic.

In the second case the tumour was shelled out from its capsule, which was seen to be continuous with what was identified as the cervical sympathetic at the time of operation. There were no signs of sympathetic paralysis after the operation.

Dr. G. W. Nicholson, who reported on the histological characters of the tumours, considers that they were identical with other ganglion neuromata of the sympathetic, although no ganglion cells were seen in the particular sections examined.

Ganglion neuromata in the sympathetic chain appear to be exceedingly rare. In 1915 Dunn\* collected particulars of these tumours. He could find only four references to cases occurring in the cervical sympathetic and six cases (four of which were doubtful) in the thoracic region, whilst he found a much larger number in connection with the abdominal sympathetic and suprarenal bodies.

In 1919 Mr. R. Davies-Colley removed a similar tumour from the cervical sympathetic in a woman. In this case an adjacent lymphatic gland, which was removed, was found on section to contain a deposit which was histologically identical with the main tumour, but there were no signs of recurrence clinically three years later.

A case was reported by Sommerfelt† in 1920, in which "a ganglion neuroma was removed from the neck of a woman of thirty-six. It had developed in the course of ten years."

The rarity of these tumours makes the clinical recognition unlikely, but if their somewhat characteristic signs and symptoms are borne in mind, a correct diagnosis should be possible, as evidenced in the second case reported above. The position deep in the neck under the sterno-mastoid muscle; the soft consistency and absence of tenderness on palpation; the absence of any infiltration of the surrounding tissues (which makes the presence of an inflammatory or malignant neoplastic tumour unlikely); and lastly, the free mobility from side to side, but limited mobility in an up and down direction—all these physical signs seem to make up a complex, which it is difficult to imagine could be simulated by other tumours.

I have to thank Mr. E. G. Slesinger for permission to publish these notes on his cases, and I am also indebted to Mr. R. Davies-Colley for allowing me to make use of the notes on his case.

\* J. S. Dunn: *Journ. Path. and Bact.*, xix., 456, 1915.

† L. Sommerfelt: *Journ. Amer. Med. Ass.*, 1238, 1920.



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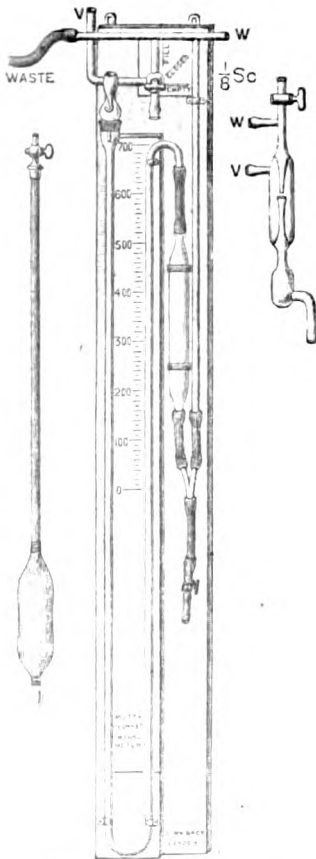
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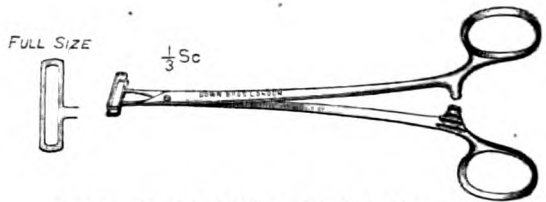
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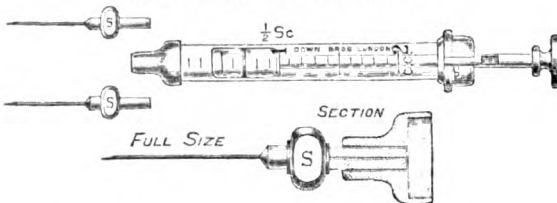
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## OBSERVATIONS ON TWENTY-NINE CASES OF ADDISON'S DISEASE TREATED IN GUY'S HOSPITAL BETWEEN 1904 AND 1923

By J. J. CONYBEARE, M.D., Assistant Physician to Guy's Hospital, and  
G. C. MILLIS, B.Ch.

ADDISON in his original communication,<sup>1</sup> entitled *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, expresses the opinion that the disease later known by his name is by no means of rare occurrence, and in his book he quotes eleven cases. Of these, however, Wilks was prepared to accept only five as true examples of the disease. By the year 1865 Wilks<sup>2</sup> had succeeded in collecting thirty-three proved cases. Since this date no collected series of the cases of the disease in Guy's Hospital have been published. A study of the cases of Addison's disease during the twenty-year period from 1904 to 1923 inclusive fails to bear out Addison's opinion that the disease would be found to be a relatively common one. During this period there have been only twenty-nine cases proved by autopsy to be true Addison's disease. In addition there are a number of cases which at some period during life were so diagnosed, but in whom autopsy demonstrated that the diagnosis had been at fault. Some of these latter will be referred to later. Apart from the cases proved at autopsy, notes have been found of a small number of other cases, where the clinical symptoms were typical of the disease, but where either death did not occur in hospital or a post-mortem was refused.

Of the twenty-nine cases proved by autopsy to be Addison's disease, twenty were males and nine females. In more than half the cases death occurred between the ages of twenty and forty. Two were under ten years of age and none above sixty. Thus the sex and age incidence does not differ materially from that found in other collected statistics.

### *Post-mortem Findings in Twenty-nine Proved Cases of Addison's Disease*

Many different pathological conditions of the suprarenal bodies have been described in the literature as causing Addison's disease, but in the present series we have only found cases of

## 370 OBSERVATIONS ON TWENTY-NINE CASES

fibro-caseous tuberculosis or simple atrophy. In the post-mortem records at Guy's Hospital there are a number of cases where other lesions, such as amyloid change, hæmorrhage, and growth were found in the suprarenals at autopsy, but in none of these cases, except two, were there any of the typical symptoms of the disease. Of the two cases in question, one had active phthisis with considerable amyloid change in the suprarenals, which, however, still showed some normal tissue. The other was a patient with bilateral hypernephroma and secondary deposits in the lungs. The patient with amyloid disease showed some buccal pigmentation and had a blood pressure of 70 mm. of mercury. The case of hypernephroma had pigmentation of the vulva and cervix only and a low blood pressure. Neither of these cases, however, had been diagnosed as Addison's disease during life.

Of the twenty-nine typical cases the suprarenals were found to be tuberculous in twenty-two, or 76 per cent., while in seven cases, or 24 per cent., the suprarenals appeared to be in a condition of simple atrophy, which in one case was so complete that a careful search failed to reveal any evidence whatever of either suprarenal. All the tuberculous cases showed a fibro-caseous condition of the glands.

Of the twenty-two cases with tuberculosis of the suprarenals, six showed an active tuberculous process elsewhere. In one case there was a tuberculous kidney and active phthisis. The remaining five cases showed general miliary tuberculosis. Only four cases with fibro-caseous disease of the glands failed to show tuberculous lesions elsewhere. There were, however, in practically every case, scars of old tuberculous lesions in the lungs, but as this is so constant a finding in post-mortem examinations of town-dwellers, no special stress can be laid on it.

The cases with atrophy of the suprarenals, on the other hand, show remarkable freedom from tuberculous lesions. In only two out of the seven cases was there old tuberculous scarring in the lungs, and in no case any evidence of active or recent tubercle.

### *Symptomatology*

The most striking point which emerges from the study of the twenty-nine proved cases appears to be that in those of tuberculous origin the duration of the disease, at any rate in its well-developed forms, is of exceedingly short duration. In only three cases had symptoms started more than one year before death, and no patient had survived more than two years

with symptoms. Of the remaining cases the average duration of symptoms was only just over four months. Many of the patients died within a few days of admission to hospital.

The seven examples of Addison's disease due to atrophy of the glands form a remarkable contrast to the above. Of the seven cases one had shown symptoms for ten years, one for five years, and two for over a year. The remaining three cases had a duration of nine, four and three months only, but in one of these death appears to have been accelerated by an acute infection. Naturally it cannot be assumed that the pathological processes in the suprarenals, whether they be tuberculous or atrophic, did not commence before the onset of symptoms. In all probability symptoms do not manifest themselves until the glands are largely destroyed. This would explain why growths involving the suprarenals are so commonly found at autopsy without any evidence of Addison's disease.

Cases of Addison's disease without pigmentation have frequently been recorded, but in the present series only two such cases have occurred. In one of these the suprarenals were atrophied and in the other there was a fibro-caseous condition of the glands. Absence of pigmentation in the mouth is, however, by no means rare. Of the twenty-nine cases eight showed no buccal pigmentation, while two patients had pigmentation in the mouth alone. All the typical forms of pigmentation, such as a generalised bronzing, pigmentation in the flexures and friction areas, and isolated pigmented spots, have been found among the cases in the series.

Asthenia seems to have been remarkably constant and as a rule had been the symptom of longest duration. Gastro-intestinal symptoms, though practically always present, usually in the form of vomiting, have occurred in most cases for a comparatively short period before death. In most cases vomiting became severe and intractable as a terminal event. In all probability it is due to failure of the circulation. Fractional test-meals were carried out in four cases only. In none of these was there anything peculiar except some degree of hypochlorhydria.

Unfortunately blood examinations were made in only five cases; in none was the hæmoglobin below 50 per cent. In most of the patients there was no evidence of severe anæmia. This is in striking contrast to Addison's views on the disease, as he puts anæmia among the leading and characteristic features.

In most of the cases a large number of estimations of the systolic blood pressure had been made. In only two instances was a blood pressure of over 100 mm. recorded, and in one of

## 372 OBSERVATIONS ON TWENTY-NINE CASES

these it subsequently fell to 80. Low systolic pressures are frequent, the lowest recorded being 40.

### *Treatment*

Nearly all the patients had treatment with adrenalin or suprarenal extract. The adrenalin was administered either by mouth or by injection. There appears to be very little evidence that it produced any definite improvement by whatever route given. On the other hand, in several cases when given by mouth it aggravated the vomiting. In one case injection of 5 minims of 1 in 1000 adrenalin produced a transient rise of blood pressure of about 20 mm.

In one case an attempt was made to graft a foetal suprarenal gland into the testicle, but the patient died within twelve hours of the operation. In another case, which was clinically typical of Addison's disease, and in which unfortunately no autopsy was possible, a foetal suprarenal gland was grafted into the kidney, again with an almost immediate fatal result. In this connection it is interesting to note that four cases either died immediately after an operation or appear to have suffered an aggravation of symptoms. One patient died within a few hours of extraction of teeth under gas, and another on the day following tonsillectomy. It would thus appear that the risks of operation are extremely great in any patient suffering from Addison's disease, and it is doubtful whether any attempt at grafting can be regarded as justifiable, particularly as there is no experimental evidence of the viability of a homologous suprarenal graft.

### *Diagnosis*

Although in theory there would not appear to be any real difficulty in the diagnosis of Addison's disease, examination of the reports of cases so diagnosed during life has in several instances revealed a faulty diagnosis. On the whole there appears to have been a tendency to diagnose the condition rather too readily. On the other hand, in a few cases the disease was found at autopsy when it had not been seriously suspected during life. The latter cases naturally were those in whom pigmentation was either slight or absent.

No single symptom can really be regarded as diagnostic of Addison's disease. Several cases of marked pigmentation, including pigmentation in the mouth, subsequently were found to be Addison's anæmia. Other pigmented patients were eventually proved to have derived their pigmentation from non-European ancestors, and in some cases the pigmentation was



probably due to chronic intestinal intoxications. Nor is the low blood pressure diagnostic in itself. Apart from the fact that occasionally a true case of Addison's disease may have a systolic pressure of 100 mm. or over, it is not at all uncommon to find a low blood pressure in patients with chronic diseases, particularly if they have been in bed for some time. In conjunction with Dr. A. A. Osman we have estimated the systolic blood pressure in a consecutive series of one hundred and eight patients, who were in the medical wards of Guy's Hospital suffering from a large variety of diseases. In no less than twenty-eight of these cases was the pressure below 100 mm., the lowest readings being between 70 and 80 mm. in patients who were certainly not suffering from Addison's disease.

Asthenia also, though undoubtedly a marked feature of most of the cases of Addison's disease, is so common a symptom of other conditions as not to be of any peculiar significance apart from confirmatory evidence. Vomiting, though apparently constant, appears usually only late in the course of the disease.

It is therefore almost impossible to be certain of the diagnosis until confirmation by autopsy. The following cases are interesting as illustrating this fact.

*CASE 1.—A Case of cirrhosis of the liver with marked pigmentation and anæmia*

Charles C., aged 41, a motor-bus driver, began to suffer from gradually increasing asthenia in January 1920, with occasional attacks of vomiting. At the same time it was noticed that he was becoming pigmented, and when first seen at Guy's Hospital in November 1920 he was diagnosed as an undoubted case of Addison's disease. He then showed marked general pigmentation, including small patches in the mouth. The spleen and liver were palpable. When first seen the blood pressure was 120 mm., but while under observation in hospital fell to 80 mm. Soon after admission a test-meal showed complete achlorhydria. This finding was confirmed on several later occasions. In March 1921 a suprarenal gland removed from a man who had just died as the result of an accident was grafted into the subcutaneous tissue of the abdomen. The wound unfortunately became septic, and in April 1921 a further graft, removed from a foetus just after death, was inserted into the substance of the left testicle. Following these operations the patient developed a severe anæmia, the hæmoglobin falling to 28 per cent. in May 1921. He was given a blood transfusion and steadily improved as regards the anæmia, and the blood pressure rose to 115 mm. by February 1922, although the pigmentation remained unchanged. The case was still considered to be one of Addison's disease in conjunction with Addison's anæmia, and he was shown at the Clinical Section

of the Royal Society of Medicine <sup>3</sup> in February 1922, and was generally accepted by those who saw him there as a genuine case of the disease, showing benefit from a suprarenal graft. The blood pressure remained between 100 and 120 mm. during this time, but for a short period there was a considerable quantity of blood passed per rectum. In June 1923 he was again admitted to Guy's Hospital, more deeply pigmented than ever, with very marked asthenia and a blood pressure of about 90 mm. He had again developed a severe anæmia with a hæmoglobin of about 30 per cent. and a red cell count of 1,200,000 per cub. mm. In many features the blood picture now resembled that of Addison's anæmia, and the spleen and liver were still palpable and hard. He had also considerable ascites. As there was no improvement, the spleen was removed, but the patient died shortly afterwards. No excess of iron could be demonstrated in the spleen. At autopsy the suprarenals were found to be perfectly normal both by naked eye and microscopical examination. The liver was markedly cirrhotic and gave the ferricyanide reaction. Examination of the left testicle, into which the foetal suprarenal had been grafted about two years previously, showed replacement of the testicular substance by fibrous tissue, with no evidence of any suprarenal tissue visible on microscopic examination. The diagnosis made at autopsy was cirrhosis of the liver, possibly with Addison's anæmia.

CASE 2.—*Case of Addison's anæmia and phthisis with marked pigmentation*

Fred P., aged 42, was admitted into Guy's Hospital in May 1911 with cough, asthenia and pigmentation, including pigmentation of the buccal mucous membrane. The blood pressure on admission was 120 mm. but rapidly fell to about 90 mm. A tentative diagnosis of Addison's disease was made. While in hospital he developed definite signs of phthisis with tubercle in the sputum. A severe anæmia developed with a hæmoglobin percentage of 29 and a red count of 1,200,000 per cub. mm. The blood film showed changes typical of Addison's anæmia. At autopsy revealed active phthisis, a large liver with a well-marked Prussian-blue reaction, which was also found in the spleen and kidneys, and the bone marrow was bright red. The suprarenals were normal macroscopically. The case appears quite definitely to have been one of Addison's anæmia and phthisis with marked pigmentation.

We have found notes of two cases in which Addison's disease had been diagnosed before admission on the strength of pigmentation, which was almost certainly hereditary in origin. One of these was a sailor who was admitted with weakness and anæmia. He was much pigmented, particularly over the shoulders, around the nipples and scrotum, and in the mouth.

A diagnosis of Addison's disease had been made in another hospital. On examination it was found that he was suffering from considerable hæmorrhage from hæmorrhoids, which had been going on for some months. These were dealt with by operation and in two months the symptoms had completely disappeared. On inquiry it was found that the patient had been born in Smyrna, and there can be little doubt that his pigmentation was due to the fact that he was not of pure European descent. The second case was somewhat similar. A woman aged 40 was admitted for weakness and pigmentation, which had been diagnosed elsewhere as Addison's disease. On inquiry it was found that her grandmother had been an Indian. The patient had always been a chronic invalid and was probably suffering from phthisis.

## REFERENCES

<sup>1</sup> T. Addison: *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, London, 1855.

<sup>2</sup> S. Wilks: *Guy's Hospital Reports*: Third Series, xi. 23, 1865.

<sup>3</sup> A. F. Hurst, W. E. Tanner and A. A. Osman: *Proc. Roy. Soc. Med.* (Clinical Section), xv. 19, 1922.

# METHÆMOGLOBINÆMIA

By N. L. LLOYD, Medical Registrar, Guy's Hospital.

## DESCRIPTION OF A CASE

D. S., a nurse, aged 26, was admitted to Guy's Hospital under the care of Dr. A. F. Hurst in July 1923, complaining of attacks of abdominal pain associated with cyanosis.

Except for typhoid fever when fourteen years old she had had no previous illness of importance.

In March 1921 she strained herself through lifting a patient, and for three weeks had attacks of abdominal pain at irregular intervals. The pain lasted from twenty minutes to three hours, and was of a stabbing nature followed by a dull ache. A laparotomy was performed and the appendix, which was found to be slightly inflamed, was removed. An "ileal kink" was also straightened out.

Following the operation she had several attacks of vomiting but less pain. She returned to duty, but pain and vomiting continued, and she began to have attacks of cyanosis.

Six months after the first operation it was decided to operate again, but she collapsed under the anæsthetic and was hurried back to bed, nothing being done.

Subsequent to this the attacks of cyanosis and abdominal pain recurred at irregular intervals up to the time of her admission to Guy's Hospital.

Her periods had always been irregular and painful, but since her operation in October 1921 she had only menstruated three times, and these periods were each followed by a cyanotic attack.

Just before some of her attacks she passed a little blood per rectum. She had always been constipated.

Since March 1921 she had noticed that she was somewhat short of breath on occasions after exertion.

During her stay at Guy's she had several attacks of pain lasting from six hours to three days. In a typical attack she experienced for some hours abdominal pain sufficiently severe to keep her awake. The pain gradually increased in severity and she became giddy. Shortly after this, cyanosis commenced

and increased gradually in degree, her respiration became rapid, shallow and thoracic in type, and she was in great distress. The cyanosis increased to an ashen-grey colour and she appeared to be *in extremis*. After a time the attack began to wear off, pain disappearing first, then abdominal tenderness, and lastly the colour returned to normal. She then rapidly recovered and was as well as ever. There was, as a rule, a slight rise of temperature at the height of an attack, reaching 101° to 101°·5 F.

Drugs seemed to have little effect. Morphia obscured the pain, but did not lessen the cyanosis. Tincture of hyoscyamus in repeated doses seemed most effective. Oxygen made no appreciable difference either to her colour or to her dyspnœa.

Between attacks she was fairly well, her general condition improving up to the commencement of another attack.

An examination of her blood showed hæmoglobin 86 per cent. and red cells 5,000,000 per cub. mm., giving a colour index of 0·86. Methæmoglobin, but no sulph-hæmoglobin, was found by Dr. J. H. Ryffel during an attack. Between attacks there was no abnormal pigment present in the blood. Blood culture was negative.

The blood pressure was found to be constantly low, the average systolic pressure being 105 mm. Hg., and diastolic 65 mm. Hg.

The x-rays showed nothing abnormal in the chest, stomach, or duodenum. On one occasion, during an attack, the ileum was thought to be in a definite state of spasm, but this condition was not observed again.

No other evidence of disease was found.

As it was thought that this might be a condition of sulph-hæmoglobinæmia in spite of the spectroscopic findings, large doses of bismuth oxychloride and of iron were given, with the object of combining with all the hydrogen sulphide in the alimentary tract, and so preventing its absorption into the bloodstream. No benefit, however, resulted from these measures.

Owing to the continued severity of the abdominal pain another laparotomy was performed in December 1923. It was found that the middle of the transverse colon was bound firmly to the base of the cæcum at the point of the old appendix scar. The adhesions had fixed the ascending colon in such a position that there was a double "hair-pin" bend, consisting of the ascending colon and the first part of the transverse colon. These adhesions were freed and the redundant omentum removed. The patient took the anæsthetic well, and made an uneventful recovery.

Subsequent to the operation she was quite well for three weeks, a length of time which was most unusual. She was, in fact, much better than she had been during the whole of her stay in hospital.

At the end of this time she menstruated slightly, the first time for ten months, this being associated with a certain amount of discomfort.

A few days later another attack of cyanosis occurred. This differed from her previous attacks in that she did not suffer from the abdominal pain, which had been such a characteristic feature before. The cyanosis lasted for about thirty-six hours and was accompanied by a headache, which was situated chiefly in the occipital region. After the cyanosis passed off the headache persisted and was so severe that she was unable to control herself.

The effect of this attack, which occurred after the operation upon which she had pinned so much faith, was seen in severe mental depression with nervous exhaustion, and for this condition she was removed to Bethlem Royal Hospital.

She had definite aural hallucinations, the voices making derogatory remarks about her. Her cerebration was in consequence rather sluggish, while her whole attitude and expression were those of a person who was, so to speak, "listening in." At the same time she suffered from tic-like movements of her head and face. There were at this time no physical signs of organic disease.

Steady improvement occurred, but eight weeks after her last attack, after severe exertion, she complained of abdominal pain, and on examination she was found to be very tender in the right iliac region. Next day she became cyanosed and breathless, the abdominal pain continuing with the same intensity. This condition disappeared completely on the following day. On inquiry, I found that this attack had, as in the previous one, been preceded two days before by menstruation.

She was discharged "Recovered" at her own request a fortnight later.

I saw her again two months later, and she professed to be "wonderfully well" and "her own self again," and was very anxious to return to her nursing. She had had one attack since leaving Bethlem—a slight return of the cyanosis, which cleared away very quickly, the only discomfort being a slight transient headache. This, again, was preceded by a menstrual period.

I could find no evidence of organic disease, although exertion

still produced a certain amount of shortness of breath. Her systolic blood-pressure was 150 mm. Hg., and diastolic 115 mm. Hg.

#### METHÆMOGLOBINÆMIA AND SULPH-HÆMOGLOBINÆMIA

Within the last twenty years there have been several references in the literature to cases of intense cyanosis, in which there were no physical signs of organic disease in the pulmonary or cardio-vascular systems, and which were not due to the taking of drugs. These cases have been described under various titles according to the author's belief as to their underlying pathology.

The first cases were described in 1902 by Stokvis<sup>1</sup> and Talma,<sup>2</sup> who considered the cyanosis to be due to methæmoglobin, but Hijmans van den Bergh<sup>3</sup> in 1905, in a careful study of two such cases, was able to distinguish two types of this condition, which had been known, and indeed is still known, as "enterogenous cyanosis." He was able to show in a manner to be described, that in one of his cases the cyanosis was due to sulph-hæmoglobin, in the other to methæmoglobin, circulating in the blood. Up to that time there had been no differentiation between the two types, and some doubt therefore arises as to the true nature of the cases described by Stokvis and Talma. The latter had already shown that the abnormal pigment was carried by the red cells and not by the serum.

Van den Bergh's work was thus of great importance in showing that two conditions easily distinguishable by simple methods had previously been described under the single name of "enterogenous cyanosis."

Since this time several authors have reported individual cases and summarised those cases previously reported, but latterly interest has chiefly been shown in the condition of sulph-hæmoglobinæmia.

#### CASES OF METHÆMOGLOBINÆMIA PREVIOUSLY RECORDED

The number of cases of methæmoglobinæmia to be found reported in the literature is small. Excluding those cases which were recorded by Stokvis and Talma (since there is some doubt as to their true nature) there have been four cases of undoubted methæmoglobinæmia reported. This alone justifies the publication of this case. The following is a résumé of the cases previously recorded :

1. *Van den Bergh's Case.*<sup>3</sup>—A man, aged 25, who had complained for seven years of weakness, cyanosis, and œdema, with diarrhœa and constipation intermittently. He was unrelieved by treatment, although a diet of milk produced temporary improvement.

2. *Van den Bergh and Gutterink's First Case.*<sup>4</sup>—A man, aged 81, with a four years' history of dysentery, headache, a feeling of paralysis of legs and arms, and cyanosis. Temporary benefit again resulted from a diet of milk, but no permanent improvement was produced.

3. *Van den Bergh and Gutterink's Second Case.*<sup>4</sup>—A man, aged 51, with a history of diarrhœa, headache, feeling of paralysis and collapse. Milk again produced slight improvement.

4. *Gibson and Douglas's Case.*<sup>5</sup>—A woman, aged 36, with a three years' history of weakness, headache, cyanosis and diarrhœa. In this case there was a history of having been addicted to drugs of the aniline group.

It has long been known that certain drugs and poisons may bring about an alteration in the hæmoglobin in the red cells within the body. This is particularly characteristic of the aniline derivatives. A few fatal cases of aniline poisoning have been reported in France, due to the use of a "patent" for staining boots and shoes. In these cases the chief symptoms were most marked cyanosis, extreme difficulty of breathing, and signs of cardio-pulmonary distress.

Dittrich,<sup>6</sup> in an investigation of toxic methæmoglobinæmia, found that in slight degrees of this condition the methæmoglobin formed was contained within the red cells, but that in extreme cases the red cells were destroyed and methæmoglobin was set free in the serum. When the methæmoglobin is all contained in the red cells the pigment seems capable of being changed once more into oxyhæmoglobin, but once methæmoglobin is set free in the serum the red cells are seen to be deformed and shrunken and are no longer capable of being restored. In such a case the abnormal pigment is dealt with by the liver, being converted into bile-pigment, and any excess not dealt with in this way may escape through the kidneys and be found as such in the urine.

It should be noted, however, that normal blood passed in the urine, if exposed to the air for a short time, has its hæmoglobin quickly changed to methæmoglobin.

In all these cases, with the exception of that reported by Gibson and Douglas, the use of such drugs had been excluded.



## SULPH-HÆMOGLOBINÆMIA

The parallel condition of sulph-hæmoglobinæmia has formed the subject of several papers in recent years and will not be discussed in detail here. Reference, however, may be made to the paper by Mackenzie Wallis,<sup>7</sup> who, in an attempt to elucidate the pathogenesis of sulph-hæmoglobinæmia, followed the suggestion of Steensma<sup>8</sup> and van den Bergh and Gutterink,<sup>4</sup> who had found the presence of nitrites in the blood in cases of methæmoglobinæmia. He found in the saliva of four patients suffering from this condition a nitrite-producing bacillus, and further that the serum of each patient contained a body capable of reducing oxyhæmoglobin to hæmoglobin. Wood Clarke and Hurtley<sup>9</sup> demonstrated in 1907 that the addition of nitrites to blood greatly accelerated the formation of sulph-hæmoglobin in the presence of hydrogen sulphide. Wallis therefore put forward the attractive theory that the disease depended upon the absorption of nitrites from the saliva, perhaps through the buccal mucous membrane, and of small quantities of hydrogen sulphide from the colon. His results, however, have not been confirmed by Long and Spriggs,<sup>10</sup> nor by Mason and Conroy.<sup>11</sup>

## DIAGNOSIS

The two conditions may be differentiated by an examination of the blood by means of a spectroscope.

The blood may be hæmolyzed by adding it to distilled water, or defibrinated blood may be used in suitable dilution. Long and Spriggs found that a dilution of 1 in 20 to 1 in 30 was the most satisfactory. Differentiation between the two spectra is scarcely possible even in the hands of an expert, except by accurate measurement of the position of the band in the red. The positions of the respective bands are as follows :

Methæmoglobin	.	.	620 to 645.
Sulph-hæmoglobin	.	.	610 to 625.

In the cases recorded by Wood Clarke, Wallis, and Long and Spriggs the wave-length of sulph-hæmoglobin was slightly increased, being 615 to 630.

The action of ammonium sulphide is a valuable aid in the further distinction of the two pigments : when a small quantity of this substance is added to blood containing methæmoglobin the band disappears, as happened in the case reported here,

whereas that of sulph-hæmoglobin is not affected except by an excess of the solution. This test was described by van den Bergh in 1905, and was apparently previously unknown to him, although it was described in detail by MacMunn <sup>12</sup> in 1880.

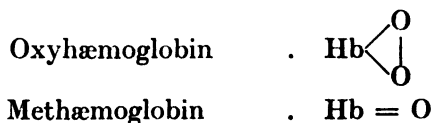
A further test was described by Wood Clarke and Hurtley,<sup>9</sup> who showed that when carbon monoxide is passed through a solution of sulph-hæmoglobin all the bands in the spectrum are moved towards the violet, the bands of oxyhæmoglobin being replaced by bands similar to those of carboxyhæmoglobin. In the case of methæmoglobin, however, no such change occurs.

#### THE FORMATION OF METHÆMOGLOBIN

The relationship between the formulæ of oxyhæmoglobin, methæmoglobin, and hæmoglobin is a matter which is still awaiting solution. Most authors are agreed that there is one atom of oxygen in a molecule of methæmoglobin and two atoms in a molecule of oxyhæmoglobin.

The oxygen in oxyhæmoglobin can easily be dissociated by exposure to a vacuum, the fluid being seen to give off bubbles of gas. In this dissociation each gramme of oxyhæmoglobin gives off 1.34 c.cm. of oxygen, an observation which indicates that there are two atoms of oxygen in the body. This dissociation also takes place if reducing agents such as Stokes' fluid (a solution of ferrous sulphate and tartaric acid made alkaline with ammonia) be added to the fluid.

By means of reducing agents methæmoglobin can also be reduced to hæmoglobin, from which, by shaking with air, oxyhæmoglobin can be formed. Methæmoglobin cannot, however, be reduced to hæmoglobin by exposure to a vacuum as happens with oxyhæmoglobin, and this fact would seem to show that the oxygen is in a different state of combination. Assuming the proportions of oxygen to be that which is generally held, the composition of the two bodies may be represented as follows :



the latter representing a more stable compound.

The change from oxyhæmoglobin to methæmoglobin must, however, involve more than the mere dissociation of one oxygen atom. It is generally assumed that two distinct events take

place. First the whole of the oxygen is removed from the oxyhæmoglobin molecule, forming hæmoglobin, and then one atom of oxygen is added to the hæmoglobin, forming methæmoglobin.

This is well shown if potassium ferricyanide is used as the agent. The whole of the oxygen in loose combination is driven off, giving rise to hæmoglobin, which is then oxidised to methæmoglobin at the expense of the ferricyanide, which is reduced to potassium ferrocyanide.

It would be of interest to know to what extent the hæmoglobin can be converted into methæmoglobin before the pigment becomes extra-corpuseular. We have little information upon this subject, but in a case of sulph-hæmoglobinæmia West and Wood Clarke found that a dilution of 0·00008 gramme of hydrogen sulphide in 10 c.cm. of mixed blood and water was sufficiently concentrated to give a definite spectroscopic appearance of sulph-hæmoglobin.

#### PATHOGENESIS

The underlying pathology of this condition is still awaiting discovery. That the alimentary tract is at fault in some way seems almost certain. The previous cases reported all showed some definite sign of intestinal trouble, while the abdominal pain which was such a feature of the case here recorded and the fact that the straightening of the ascending colon has seemed to result in almost complete relief leave the matter in little doubt.

We have again little information as to how the pigment, once formed, is again turned back into an oxygen carrier. The rapidity with which the colour disappeared in this case was very striking, and yet at no time was there any evidence of abnormal pigment in any of the excretions.

The relation of the attacks to menstruation was also sufficiently striking to be worthy of special mention. There is a condition found rarely in puerperal infection, and described by Schottmüller and Bingold, in which methæmoglobin, hæmatin, and sulph-hæmoglobin have all been found in the blood. It is difficult to know whether there is any connection between such cases and the case described here.

#### TREATMENT AND PROGNOSIS

The previous cases described were all benefited by a diet consisting largely of milk. None of them, however, improved

for any length of time. The case reported here was not, as far as could be judged, benefited in any way by such treatment.

It is early as yet to talk of the ultimate prognosis of this case. So far, however, the patient has not shown any signs of further trouble. It is to be hoped that the condition of the abdomen which was relieved was the cause of the whole trouble, and that with this put right she will have no further symptoms.

I am indebted to Dr. A. F. Hurst for permission to publish notes on this case, and also to Dr. J. G. Porter Phillips, of Bethlem Royal Hospital, for information as to the patient's condition while under his care.

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## A CASE OF ARACHNO-DACTYLY WITH SPECIAL REFERENCE TO OCULAR SYMPTOMS

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### DESCRIPTION OF CASE

TIMOTHY K., aged 12, was sent to one of us (A.W.O.) by Dr. Alfred Salter with a request that an attempt should be made to try and improve his vision with glasses and for an opinion as to any treatment which might benefit his sight. As the boy's appearance was so strikingly abnormal he was considered to be a case of more than purely ophthalmological interest. Permission was obtained from his parents to allow him to stay in the hospital for a short time in order that certain examinations might be made and records taken.

A careful inquiry into the family history revealed no evidence of hereditary organic disease. The patient is the youngest of three children, having two brothers aged 18 and 16 years respectively. He was a full-term child, born in a difficult labour and breast-fed for six months. Though not weighed at birth, he was noticed to be thin. Apart from measles when 3 years old, he has had no illness of note, though when  $2\frac{1}{2}$  the patient was so unusually thin that he was taken to a doctor and treated for tuberculosis. He attended school for a little more than a year, but owing to defective vision he made little progress and ceased attendance when aged 7. At this time treatment for his eyes commenced. "Needling" of his right eye was performed at Moorfields in 1920, and on three subsequent occasions at the same hospital.

The boy volunteered the information that he is subject occasionally to attacks of sickness, headache and loss of appetite. His mother in her youth was similarly affected. These attacks can be accurately called cyclical vomiting.

As a result of his visual defect the patient has not learnt to read or write, but considering his illiteracy he is remarkably intelligent. He takes an active and useful part in domestic activities.

It is seen on examination that the patient is tall and thin. His height is  $6\frac{1}{2}$  inches greater and his weight 18 lbs. less than

the normal figures for a boy of his age, taken from the Report of the Royal Commission on Physical Training (Scotland,



FIG. 1.



FIG. 2.

Figs. 1, 2, 3. Photographs of Timothy K., aged 12, showing several of the abnormalities described in the text.

1903). The head is markedly dolichocephalic, the thorax narrow and flat (chest measurement in nipple line  $22\frac{1}{2}$ — $23\frac{1}{2}$

inches), the hands and feet narrow but disproportionately long. The width of the hand at the metacarpo-phalangeal joint is  $\frac{1}{4}$  inch less, whilst the length of the hand (mid-point of wrist joint to tip of longest digit—medius) is  $1\frac{1}{2}$  inches greater than the measurements taken in a boy of normal height when aged 12. The ratio of the length of the hand to the length of the limb is 2.95; that of the normal being 2.71. The lower limb is similarly disproportionate. A rough idea of the unusual length of the foot can be gathered from the fact that though only 12 the boy wears boots size VI! The extreme thinness of the limbs and trunk can best be appreciated from the photographs (Figs. 1, 2 and 3).

The following is a list of the additional abnormalities which this patient shows: a highly arched palate, an abnormal conformation of the pinna (Fig. 4) (a prolongation of the crus of the helix so as to produce a well-marked ridge on the concha); bilateral iridodonesis, with a dislocated lens in the left eye, the right lens having been absorbed as a result of operations; absence of subcutaneous fat; some degree of acro-cyanosis; "winged" scapulæ; rather prominent supra-orbital ridges; coarse straight hair which "hangs like flax on a distaff"; slight bilateral contractures of the biceps, preventing complete extension of the forearms; slight scoliosis in dorsal region; slightly abnormal "webbing" of the fingers (Fig. 5);



FIG. 3.

slight upward displacement of the patellæ with apparent thickening of the lower ends of the femurs; "susceptibility" to the mydriatic alkaloids.

Routine examination of the cardiovascular system shows no special abnormality except for some cyanosis of the extremities. The pulse and blood pressure are within normal limits and respond normally to exercise. On the condition of the heart Dr. C. H. Hunt reported to the effect that it is enlarged relatively to the small size of the thorax, but there



FIG. 4.

Timothy K., showing abnormal prolongation of the crus of the helix producing a ridge on the concha.

is no actual cardiac enlargement. A functional systolic bruit may be heard in the pulmonary area, but there is no evidence of a congenital heart lesion.

Physical examination of the chest suggests the presence of enlarged mediastinal glands, particularly on the right side. Mr. Redding reporting on a radiogram of the thorax says, "simple dorsal scoliosis, some peri-hilar infiltration of the right lung rather suggestive of early tuberculosis."

The muscles are weaker than the normal, so that the patient has difficulty in maintaining any given anti-gravity posture. There is, however, no evidence of a lesion in the central or autonomic nervous systems, particularly none such as might give rise to weakening or wasting of the muscles.



Radiograms prepared and examined by Mr. Redding show slight general rarefaction of the bones of the foot with increase in length of the long bones of the hand and foot : slight general rarefaction and some irregularity of structure of the lower end of the femur, but no epiphyseal changes (Fig. 6); the

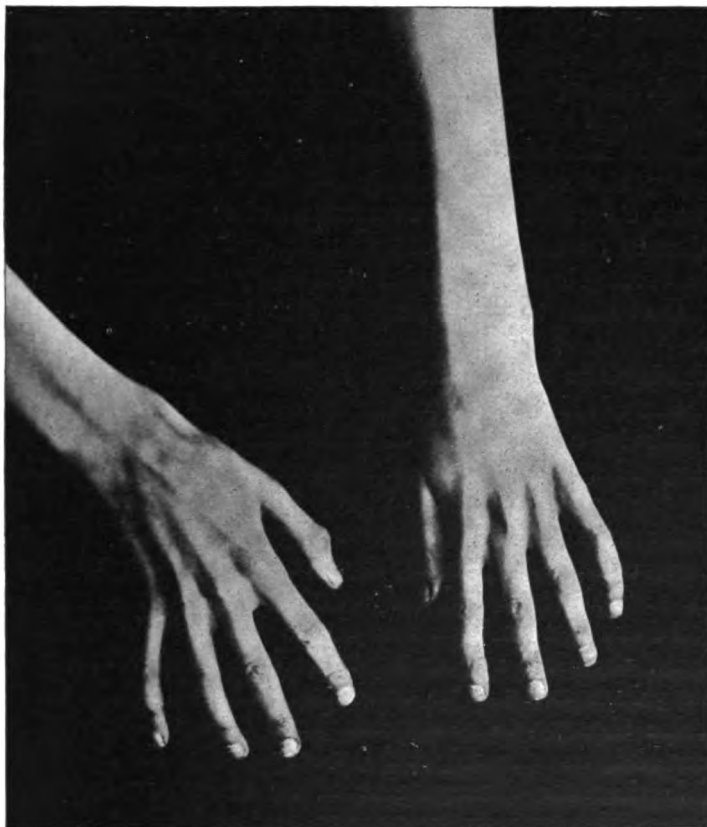


FIG. 5.

T. K. The forearms and digits are long and slender. There is a slight excess of webbing between the digits.

sella turcica shows no definite expansion. The ocular condition will be described in a later paragraph.

#### NOMENCLATURE AND PATHOGENESIS

Cases such as this have been described by different terms, including *pieds d'araigne* (spider-feet : Marfan<sup>1</sup>), hyperchondroplasia, "a case of atavism," and arachno-dactyly. Although arachno-dactyly is a name which describes only one of the many

abnormalities usually present, it is the name which is likely to be retained. Hyperchondroplasia was the name given to the condition by Méry and Babonneix<sup>2</sup> on account of the fact that in Marfan's<sup>1</sup> original case, thickening of the lower end of the femurs was found; this they attributed to overgrowth of the epiphyses. It is clear that in some ways arachno-dactyly is the antithesis of achondroplasia. In this case the slight thickening of the lower end of the femurs was not shown radiographically to be associated with hyperplasia of the epiphyseal cartilages.

In 1920 Thursfield,<sup>3</sup> after reporting a case of his own and reviewing the eight previously reported cases, dealt briefly with two theories as to the causation of the disease: (1) that it is due to an endocrine disturbance, and (2) that it is in the nature of a primary muscular dystrophy; he considered that up to that time the balance of evidence was in favour of the latter.

Viewing the former theory in the light of our case and others there is little to be said in its favour. If arachno-dactyly were merely a condition of maldevelopment of the bones, muscles, skin, hair and circulation, it would be reasonable to regard the condition as analogous to cretinism and to make diligent search for the endocrine organ at fault. There are, however, constantly present, together with these maldevelopments, several congenital malformations, such as are not seen in cretinism, but such as are almost the rule in mongolism. It would therefore appear that arachno-dactyly is analogous to mongolism and not to cretinism. The attempts to apply endocrine therapy to mongolism have been almost uniformly unsuccessful, as one might have expected; for it is inconceivable that the derangement of an endocrine organ could be responsible not only for poor mental and physical development, but also for brachycephalic skulls, abnormally oblique epicanthic folds, congenital heart lesions, cleft palate, talipes, malformations of the ear, syndactyly, etc., all of which conditions are part of the clinical picture of mongolism. Similarly it is unlikely that all the malformations associated with arachno-dactyly can be due to the absence of an internal secretion.

With regard to the view that the condition is in the nature of a primary muscular dystrophy, a similar difficulty has to be faced in correlating the characteristic symptom of muscular dystrophy—the wasting—with the striking congenital abnormalities. Further, in a typical muscular dystrophy one expects to find a definite family history and a condition which, starting

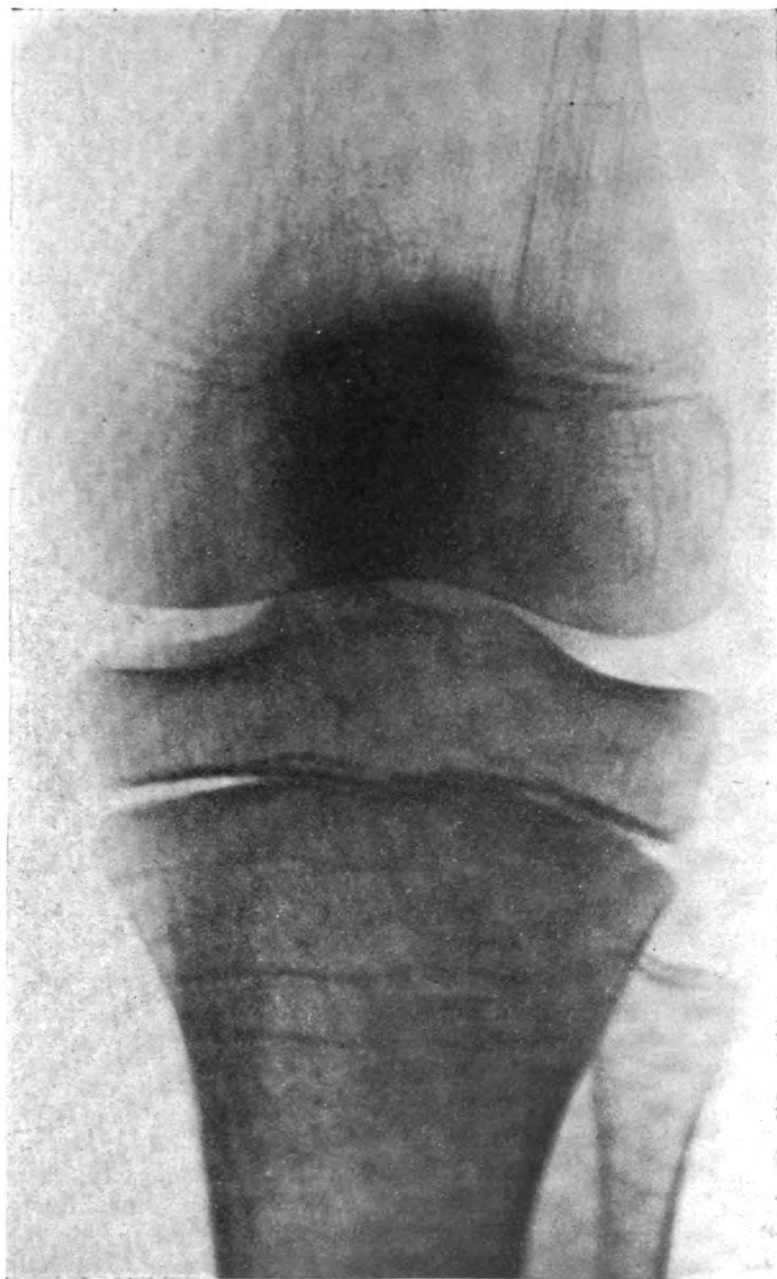


FIG. 6.

Radiogram of knee joint. Report states, "Some irregularity of lower end of femur but no epiphyseal changes."

in early youth or later, proves to be to a greater or less extent progressive. Arachno-dactyly is apparently unassociated with these phenomena. It is true that some of these patients become worse, owing to increasing contractures and scoliosis or to a lowered resistance to tuberculosis (to what extent, if any, "root phthisis" participates in the wasting in our case it is difficult to say), but the same may be said of mongols. Mongols fall ready victims to intercurrent infections, and as they grow older, develop fissured tongues, nasal obstruction due to chronic rhinitis and, later still, lamellar cataracts.<sup>4</sup> These lesions, like those of arachno-dactyly, are not in the sense of the muscular dystrophies, progressive. They are the almost inevitable results of congenital characteristics.

In 1913 Poynton<sup>5</sup> showed a case of what is now called arachno-dactyly, as "a case of atavism." It appears that it is perhaps wise to re-emphasise the atavistic factor in arachno-dactyly and to regard it as a freak of nature, not to be understood until the factors concerned in normal development are more thoroughly known.

#### OCULAR SYMPTOMS

Of the seventeen cases of which we have been able to find records in current literature, nine have notes of definite ocular symptoms. It is possible that the actual number should be larger, as in some of the records no mention of the ocular condition is made, but in others it is definitely stated that the eyes were normal.

Of the ocular symptoms the most marked are congenital dislocation of the lenses with the concomitant symptom of trembling irides, small contracted pupils, irregularly deep anterior chambers and limited reaction to dilatation by atropine. The ocular symptoms in the case of our patient are as follows.

*Right eye.*—Anterior chamber deep, iris tremulous, pupil small but active, dilates very slightly to atropine, and when atropine is pressed, marked irritation is produced. The lens is absent and only a small fragment of the lens capsule remains in the pupil. The retinal vessels were seen with great difficulty, and the reason for this was not obvious, but probably the vitreous is not clear. His vision is improved by a + 6 D. Sph., but his macular fixation is defective. He cannot see 6/60, but his field of vision appears to be full to fingers. The lens of this eye had been removed at Moorfields Hospital by Mr. Juler.

*Left eye.*—The anterior chamber is deep, the pupil small but active, the iris tremulous—atropine has very little effect on the size of the pupil, duboisine rather more. A view of the optic disc was obtained which showed a myopic crescent of large size. With a lens of  $-40$  the boy could see 6/60, and he found this lens very useful in enabling him to see to get about. There is a slight vertical nystagmus noticed at times and also divergence. The lens is probably dislocated backwards, but the pupil never dilated sufficiently to show the edge of the lens, and as the increased depth of the anterior chamber appeared to be uniform it was impossible to decide in exactly what direction it was displaced.

In Borger's <sup>6</sup> cases (Nos. 1 and 18) we find a similar condition. Case 1: iridodonesis (trembling of the iris on sharp lateral movements of the eyes or head); high myopia, and in addition persistent pupillary membrane; deeply set eyes with large orbits, and prominent supra-orbital margins.

Case 13: showed iridodonesis, with dislocated lenses; congenital hydrophthalmos; deep anterior chamber; large and deeply set eyes with nystagmus.

Pfaundler's case (Case 11) also had hydrophthalmos, tremulous irides, with dislocated lenses.

In Fowler's case (Case 2), examined by Sinclair, especial emphasis is made in the report of the difficulty of examining the fundus, as the pupils did not dilate with atropine, but no evidence of optic atrophy or other gross change was found, although a note is made in the medical report that the child had not been able to see well since birth, and at eleven months old she developed a divergent squint; that the pupils were small, that she used her left eye, holding things closely to it, and that her distant vision was better than her near vision.

In M. B. (Case 10) the following are Dr. Sinclair's notes:

R.V. with  $+18$  D. Sph. = 6/18. L.V.  $+18$  D. Sph. = 6/36. Fields of vision full. The pupils react to light. Eyes externally normal. Ocular movements normal. Right lens dislocated inwards and downwards and repeatedly found to be in the same position, though it is not fixed. Left lens dislocated downwards and freely movable with movements of the eye. The refraction of the aphakic part—about 18 diopters of hypermetropia in each eye. The fundus oculi on both sides is normal.

The only abnormalities found are dislocation of the lenses and amblyopia of the left eye, in which vision has always been relatively defective.

In Salle's <sup>7</sup> case (Case 14), an infant of  $2\frac{1}{2}$  months, with œdematous eyelids, very contracted pupils were noted, but as far as could be ascertained the optic discs and fundi oculorum were normal.

In the account published in the Medical Society's Transactions of Poynton's second case (Case 15),<sup>8</sup> "a member" stated he had a case of arachno-dactyly with dislocation of the lenses under his care, and that the general symptoms of his patient were similar to those of Poynton's.

In Marfan's case (Case 3) a note was made that one other child in the same family had congenital cataract, but the patient with arachno-dactyly did not show any ophthalmic lesions.

The consideration as to whether the occurrence of these ocular defects throws any light on the ætiology of this very obscure disease, brings us to the question, at what time in development does the defect in the suspensory ligament of the lens occur? It is supposed by Treacher Collins<sup>9</sup> that the fibres of the suspensory ligaments are originally cellular adhesions between the lens and the ciliary processes, and that as the eye grows these adhesions are stretched and lengthened out into fibres. These cases then of defective development of the suspensory ligament leading to dislocation of the lens with iridodonesis must be due to causes operating within the first three or four months of foetal life.

In foetal life—three to four months—the sides of the lens are actually connected with the ciliary body by means of cellular adhesions, but as the eyeball enlarges proportionately much more than the lens, the space is increased, and these adhesions between the ciliary body and the fibro-vascular sheath of the lens must necessarily be stretched and elongated and ultimately form the suspensory ligament. When the vitreous has enlarged, and the whole eye reached its maximum, these adhesions become stretched and elongated into fibres, which fibres keep the lens capsule taut and stretched, flatten out the lens and retain it in its position. If now for any reason the adhesion of the lens to the ciliary body is non-existent at one part, and this is almost always the lower part, the attachments of the globe above and to the circle of the ciliary processes around will draw the lens upwards and possibly inwards or outwards, leaving the lower edge of the lens unstretched, and if the gap is sufficiently wide, results in a dislocation of the lens in some upward direction. On the other hand, Dr. Ida Mann,<sup>10</sup> in a paper read before the Ophthalmological Congress held in Glasgow this year, contends that "the main factor in the production of a coloboma in the iris, ciliary body, choroid, and suspensory ligament appears to be the persistence for an abnormally long time of one, several, or all of the vessels which usually connect the circulus arteriosus iridis major with the terminal branches of the hyaloid vessel around the edge of the

optic cup. These she had named the irido-hyaloid vessels; they appeared at the fifth week in the human embryo and began to disappear in the middle of the third month, when the ectodermal part of the iris started to grow forwards in front of the lens." It appears, therefore, that these defects in the suspensory ligament which give rise to iridodonesis are due to causes which arise during the second or third month of foetal life and seem to be remote from an endocrine causation, but due rather to a developmental one. Congenital miosis has been shown by Holth and Berger<sup>11</sup> to be the result of an absence of the dilatator fibres in the iris, etc., and this may well be the cause of the miosis in these cases. So far then as the ocular symptoms are concerned we find no support for the theory that endocrine deficiency is a cause.

#### APPENDIX

The notes of seventeen cases reported in medical literature are appended as being interesting on account of the rarity of the disease and the scattered records of the cases.

1. *Borger's*<sup>6</sup> case, No. 1.—Male, 9 years old. The mother and midwife noticed that the newly-born baby was very long and thin, especially about the hands and feet. The child was always thin and hollowed-eyed, and as soon as he began to go about it was noticed that he required very large sizes in shoes. He was always short-sighted and had to wear glasses.

On examination: tall and thin for age; head relatively small, orbits large, eyes sunken. Expression—has an appearance of suffering. Extremely timid and easily frightened.

Skin normal; very little fat; hair thick and dry, nails normal. Spine shows slight scoliosis, and scapulæ are scaphoid. Bones of extremities very slight and hands and feet very long and thin. Calcaneum spur-like. Hyperextensibility of hands and feet. Musculature is poor and gait feeble. Pes planus left, double genu recurvatum.

Unusual development of the crus heliciis in the external ear. Heart dulness increased to left; loud systolic murmur at apex down sternum; pulmonary second accentuated. Intelligence normal.

Patient is 12 cm. too tall and 11·9 kilos too light for his age.

Careful measurements as compared with a child of the same age showed that in this case the relative lengths of the different bones was not much altered. They appear longer than they are on account of the thinness. The x-ray appearances show that ossification is in advance of the age. The skull showed no special abnormality of the sella turcica.

2. *Fowler's* case (we are indebted to Dr. J. S. Fowler for the notes and photographs of this case as well as of Case No. 10)—Male, aged 9 (Fig. 7). The child complains of pain on walking

any distance. He walks quite well, but with the toes pointing outwards.

*Left foot.*—Long plantar arch lost, walks on mesial surface of the sole, on the base of the first metatarsal and internal cuneiform. Tuberosity of the navicular very prominent. Both malleoli are broad and prominent. The foot as a whole is long and narrow, especially across the heads of the metatarsals. Metatarsals and phalanges are all long. Plantar flexion of three lateral (outer) toes.

*Right foot.*—Arch not completely lost. Malleoli prominent. Slight plantar flexion of three lateral (outer) toes.

*General examination.*—Very thin, and taller than average for age. Intelligence good.

*Head.*—Slight asymmetry, left frontal bones receding slightly and less prominent than right.

*Ears.*—Large, soft and deficient in cartilage. Lack of definition of antihelix.

*Eyes.*—Vide supra.

*Chest.*—Costochondral junctions prominent.

*Heart.*—Loud systolic (? congenital) murmur well heard over the whole of the præcordia. No breathlessness, cyanosis, or clubbing of the fingers.

*Back.*—Scoliosis of first degree, most evident when sitting; 5th dorsal to 1st lumbar convexity to right.

*Arms.*—With arms fully abducted he can supinate fully; when they are abducted and the elbows flexed he cannot supinate fully: can be fully extended at elbows.

3. *Marfan's*<sup>1</sup> case.—Girl, aged 5½. Unusual length and slenderness of the bones of the feet and hands. Hyperextensible joints. The os calcis was "spurred." The head was dolichocephalic, but not asymmetrical. All the limbs were longer than those of a normal child of the same age. The muscles were all atrophied but not paralysed. Patient was one of five living children, one suffering from convulsions, one from congenital cataract. Deformity was noticed at birth by the midwife. First tooth at four years; spoke at three years. Unable to walk. The patient was under Marfan's observation for three years, and no change was observed. The characteristic changes in the extremities were present, and there were contractures of the elbows and knees and also of the fingers. Depression of the skull which crossed from one ear to the other, slight cranial and facial asymmetry. Mental condition normal.

Méry and Babonneix<sup>2</sup> showed the same case six years later, when the changes were not marked except that scoliosis had been added to the kyphosis and there was an overgrowth of the epiphyseal cartilages. Neither the eyes nor the ears showed any abnormality.

4. *Dubois'*<sup>1 2</sup> case.—Girl, aged 10 years. At birth the extraordinary slenderness and length of the hands and feet were noticed. Teeth at six months. Walked (limp) at sixteen months, and spoke at eighteen months. Between five and



six years *rötheln*, and later scarlet fever, to which Dubois attributes a valvular lesion which was present. The child was always thin. Congenital dislocation of the hip was present.



FIG. 7.  
Case No 2 (Appendix). Male, 9 years, showing many of the abnormalities described in text.

Very long and slender extremities, especially distally (shown in photograph). Hammer toe on right foot. The author (? Thomas) believes that the valvular lesion was due to congenital defect, but it is impossible to be sure.

5. *Poynton's*<sup>5</sup> case.—Boy, aged 3. First case published in English and described as "a case of atavism." Congenital flexure of thighs on abdomen. "Chimpanzee" posture. Os calcis spurred. Atrophy of muscles. Ears large. Fingers and toes extraordinarily long. Eyes normal. Flat foot. Suggested diagnosis, "Muscular dystrophy of unusual type."

6. *Thursfield's*<sup>3</sup> case.—Boy, aged ? 5–6. Patient was the fourth child. The others alive and healthy. Family history not important. Long slender fingers and forearms.

Dr. Thursfield's summary of this case is as follows :

(1) Undue length and slenderness of the bones of the hands and feet.

(2) Ill-developed musculature, and muscular atony throughout the body.

(3) Contractures of the muscles and tendons, especially those of the hamstring muscles.

(4) Asymmetry of the skull and deformity of the external ear.

(5) Lastly, the tendency of the bones of the thorax to bend and assume abnormal shapes—a tendency which in the present instance was not obvious in the first year of life. Dolichocephalic skull. Scoliosis. Pupils small but otherwise eyes not grossly affected.

7. *Duperie, Dubourg and Guénard's*<sup>13</sup> case.—Female, 10 years old. Congenital deformity, long and slender hands and feet. Sense organs normal. Calcaneum spurred. Kyphosis. Muscles thin and atrophic. Prognathous. High-arched palate. Rickety rosary. Wassermann and Babinsky negative. Parents very young (F. 17; M. 16). Hip joints dislocated. Heart normal. Hypophysis defect? Eyes not mentioned.

8. *Rocher's*<sup>14</sup> case.—Reported a case similar to Duperie's case. Boy, aged 10 years. Long hands and feet. Very loose articulations. Dislocation of hips, which were reduced. Prognathous. Kyphosis. Knees flexed by contraction of thigh muscles. No mention of heart, eyes, ears, etc.

9. *Achard's*<sup>15</sup> case.—Girl, aged 18 years. This is a doubtful case, as the mother and other relatives had long fingers and hands and feet. No other abnormalities present. An eleven-year-old sister showed a similar condition.

10. *Fowler's* case.—M. B., girl (Fig. 8). Full-term child. Defective sight since birth. Divergent squint when 11 months old. Hands and fingers, also feet and toes, very long and slender. Well-grown, healthy-looking child. Ears unusually "curled." Slight contraction of muscles of forearms. Calcaneum prolonged backwards. Slight degree of genu recurvatum. Undue mobility of joints. X-ray of head failed to demonstrate any abnormality of the sella turcica, owing to the heavy breathing of the child causing movement of the head with each respiration. Good average intelligence. Eyesight affected. *Vide supra*.

11. *Pfaundler's*<sup>16</sup> case.—Female, 1 year. Kypho-scoliosis.

Talipes-calcaneus. Flat foot. Cardiac defect (congenital heart). Funnel-shaped chest. Ossification advanced to three years.

*Eyes.*—Hydrophthamos. Luxation of lenses. Tremulous iris. Appearance of senility. Large ears. Long and slender hands and feet, also fingers and toes. Hyper-pituitary, slenderness of the bones and soft parts.

Post-mortem.—No demonstrable lesion of the endocrine glands. Cf. Borger's 2nd case, No. 13.



FIG. 8.

Case No. 10 (Appendix). Female,  $2\frac{8}{12}$  years. The hands and fingers are long and slender.

12. *Thomas'*<sup>17</sup> case.—Girl, aged  $1\frac{1}{2}$  years. Hands and feet noticed at birth to be long and slender. Family history good. Could sit up but could not walk. Muscles feebly developed. Subcutaneous fat almost absent. Ears deformed, marked development of crus helices. A case of atavism. No evidence of mental defect. Child developed slowly and steadily. Slender child, weighing 5900 gr. and measuring 75 cm. Fontanelle still patent. Craniotabes present. Epiphyses of ribs, forearms, and ankles enlarged. Convolutions of ears abnormal. Eyes normal. Heart normal. Some degree of webbing of fingers and toes. Spur-like os

calcis. Radiographic appearance at two years. Three ossifications centre of wrist.

13. *Borger's* <sup>6</sup> case, No. 2.—Female, 1 year old. Four weeks premature. Abnormal length of fingers and toes noticed at birth. Nystagmus always present. Always weak and feeble.

On examination child showed striking appearance, the features being like those of an aged person; nutcracker jaw; lips small and sunken in; chin and nose prominent; nasolabial folds marked. Eyes large and deep set. Child is very feeble. Neither legs nor arms can be fully extended. Can



FIG. 9.

Case No. 15 (Appendix). Showing abnormalities similar to those seen in the other cases.

neither sit nor stand. Hands and feet very thin, and long, spur-like calcaneum. Pes planus. Hyperextensible hands and feet. Manubrium sterni projects and sternum is funnel-shaped below, marked kypho-scoliosis. Cannot be corrected. Fontanelle patent widely; no rickets. Heart—a loud systolic murmur heard all over the left axilla and to some extent on the left side also. Ears are large. Death from pneumonia.

Measurements showed that the bones were longer than normal, especially the distal ones. Ossification was advanced.

Post-mortem.—Patent foramen ovale. Only two lobes in the right lung. Examination of the bones and glands threw no light on the nature of the condition.

Commentary.—It is pathological giantism.

14. *Salle's* <sup>7</sup> case.—Boy: lived 18.7.1911 to 2.10.1911. Paper reviewed in the *British Journal of Children's Diseases*, vol. xi., 1914, p. 181.

"On a case of abnormally long extremities in an infant with an acromegalic symptom-complex." Abnormally long fingers and toes. Large nose, prominent chin, large lobes to ears, big tongue, very long fingers and toes. Eyelids œdematous. Eyes—pupils small and contracted. Ant. chamber shallow. Optic discs and retina normal.

Post-mortem revealed an enlarged sella turcica and a protuberant hypophysis, containing numerous eosinophil cells.

15. *Poynton and Maurice's* <sup>8</sup> case.—Case shown at a Clinical evening, Nov. 14, 1921 (Fig. 9). W. D.: Female, aged 16. Was first under observation in 1918, when she had measles and a commencing spinal curvature and was tall and very thin. A year later her mother noticed a flexion of the ring and little fingers. The exaggeration of growth is confined to the bones of the upper and lower extremities. Ears normal. No mention of the eyes. Scapulæ long. Arms and hands, legs and toes very long and thin. Had a loud systolic murmur dating from an attack of tonsillitis. Heart hypertrophied.

The authors remark that a very interesting feature in this case is the absence of any striking evidence of the abnormal growth of the long bones until within the last two years.

16. Case mentioned by "a member" at a Meeting of the Medical Society, Nov. 14, 1921. Precisely similar to Poynton and Maurice's case.

Aged 1 year. Very intelligent; with congenital dislocation of the lens; great length of metacarpal and metatarsal bones. Curious deep voice, improved on polyglandine treatment.

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# A CASE OF SUPRA-PITUITARY TUMOUR ASSOCIATED WITH FRÖHLICH'S SYNDROME

## WITH SOME COMMENTS UPON THE FUNCTIONS COMMONLY ASCRIBED TO THE PITUITARY BODY

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### CLINICAL HISTORY

C.C., æt. 19, a hawker, from Welling in Kent, was admitted to Guy's Hospital on July 28rd, 1923, for drowsiness and paralysis.

*Family History.* His father, mother, and nine sisters and brothers were healthy.

*History of previous diseases.* He had not suffered any previous illnesses. He had had his adenoids removed at an early age.

*Present illness.* The history was that his trouble had commenced 15 months previously, when he first complained of pain at the back of his eyes. This grew gradually more and more intense, and he found it impossible to sleep at night, and eventually had to give up work during the day. He was treated by his doctor and improved sufficiently to do an occasional day's work.

During the months that followed he had occasional fits. These consisted in a sensation of giddiness and faintness, after which he would fall.

It was for these fits that in April 1923, a year after his first symptoms, he was admitted to the West London Hospital for Nervous Diseases, and for the notes upon his condition at that time we are indebted to Dr. Harry Campbell, who has kindly allowed us to make use of them. In one of the fits observed there by the R.M.O. there was a definite aura of smell—a smell of bad fish—there being no trace of fish on the premises at the time.

Owing to the general physical make up, small genitals with hair and fat of the female distribution, dyspituitarism was suspected, but an x-ray of the skull revealed nothing definite.

*An examination* at that date revealed the following abnormalities :—

*Vision.* The fields of vision were not limited, but there was swelling of the discs to the extent of 4 diopters on the right side, and 2 diopters on the left side.

*Cranial Nerves.* There was a little ptosis of the left eyelid, and a little weakness of the left face. There was nystagmus in extreme positions.

*Motor System.* There was some tremor of the left hand, an absent left abdominal reflex, and a plantar reflex that was extensor on the inner side of the sole, and flexor on the outer side. There were no abnormalities in the other reflexes and sensation was not affected.

### *Investigations*

The cerebro-spinal fluid showed :—

Protein	.	.	0.15 per cent. (normal 0.02 per cent.).
Chlorides	.	.	0.74 per cent.
Sugar	.	.	A low normal reading.
Cells	.	.	Less than 1 per c.mm.
Wassermann—doubtful positive.			

A blood Wassermann was negative, but with slow hæmolytic. A blood count revealed nothing.

He was given a course of N.A.B. injections : 0.45, 0.45, 0.6, 0.9, 0.9 gms., and a mixture containing Hydrarg. perchlor. and Pot. iod. Surgical intervention was deemed inadvisable owing to the paucity of physical signs.

He improved greatly under treatment and returned home in seven weeks. After returning home he gradually got weaker and weaker, and soon lost the use of his limbs. Later speech became indistinct and difficult, and was finally lost, and swallowing was accomplished with the utmost difficulty. He lost control of defæcation and micturition.

He never lost consciousness, and was able to reply to questions with nodding movements of his head. Thus he denied having any headache. He never vomited, but was once seen in a fit. In this he did not lose consciousness, but his eyes were said to roll, and his face was contorted; it lasted a few minutes.

*On admission* to Guy's his condition was as follows :—

Though 19, he looked considerably younger. He was well-covered, looked healthy, and had a fresh complexion. The distribution of fat in his body was of the female type—marked in the pectoral region and on the abdomen—and he had scanty axillary and pubic hair, which again conformed to the female distribution. His genitalia were small and ill developed. Both testicles were in the scrotum.

He lay in bed motionless and expressionless, but could respond to loud exhortations by nodding or shaking his head. He occasionally made efforts to speak, but was unable to articulate.

His lips were moving constantly in a kind of smacking movement (this, it was thought, might be related to the aura of smell previously mentioned).

## 404 A CASE OF SUPRA-PITUITARY TUMOUR

He kept constantly swallowing, as though it were difficult to clear his pharynx of secretions. A gurgling noise accompanied both his respiratory movements and his attempts at swallowing.

Apart from a thick coating of fur on his tongue, nothing abnormal could be detected in the Alimentary, Respiratory or Cardio-Vascular Systems.

### *Examination of the Central Nervous System*

There was practically complete blindness.

The discs showed optic atrophy. There was no papillo-œdema.

*Cranial nerves.* Pupils failed to react to light or accommodation. Left pupil larger than right.

It was impossible to test functions completely, owing to poor responses. There appeared to be partial paralysis of most of the nerves—though this was not complete in any one.

He could move his eyes well—except directly up (III, IV, VI).

There was nystagmus on looking to right and left, or up or down.

His face was expressionless—movements weak (VII).

Partial deafness seemed to be present (VIII).

The reflex of swallowing was partially though not completely disorganised (IX, X).

He could move his tongue (XII).

The functions of I and V could not be tested.

*Motor System.* He could move his limbs a very little, and could maintain an arm uplifted for a short space of time. There was more power on the right side, though this was very slight.

*Sensation.* No impairment detected (responses poor).

<i>Reflexes.</i>	Arm jerks . . . exaggerated	} Equal on the two sides.
	Knee jerks . . . exaggerated	
	Ankle jerks . . . exaggerated	
	Ankle clonus . . . present	
	Plantar responses . . . extensor	
	Abdominals . . . absent	

*Sphincters.* He had complete incontinence of urine and fæces, and he had a large red inflamed area on his back from inattention to these defects.

On the 25th of July he was seen in a fit. His eyes were jerking in a rapid nystagmus—the quick movement being towards the left. His head rocked from side to side. His pulse fell from 120 to 44.

In a few minutes the fit passed off. All his reflexes were unaltered by the fit.

He grew daily more completely paralytic and comatose. There were remarkable variations in the rate and force of



the heart-beat from hour to hour. The rate varied from 70 at its lowest to 130 beats per minute. At one time the pulse was slow and full, at another rapid and uncountable.

His face was constantly scarlet, and he sweated profusely. He ran a slight pyrexia for a few days associated with bronchitis. This improved on vigorous treatment. Two days later the gurgling noise in the pharynx grew worse, a marked bronchial fremitus became obvious, and he died rather suddenly at 6 a.m. on the 10th of August, 1923.

The following investigations had been performed :—

Wassermann in Blood	Negative.
"          " C.S.F.	Negative.
Chemical Examination of C.S.F.	Sugar, present.
	Protein, 0.04 per cent.
	No white cells seen.
	Some red cells ( ? traumatic ).

The treatment consisted chiefly in good nursing. The bed sore improved with "Emol Keleet" applications. He was fed nasally four-hourly. He was given belladonna in order to lessen the secretions of his pharynx.

#### POST-MORTEM EXAMINATION

There were tracheitis with blood-stained fluid in the trachea and patches of inhaled blood in the lungs. The foramen ovale was not completely closed. The aorta showed early atheromatous changes. The suprarenals were small, both together weighing only 10 gms.

*Brain.* On opening the skull the brain did not appear obviously enlarged, but on removing it from the cranium there was marked distortion of its base.

A large tumour bulged in this situation, projecting in the middle line. It was fluctuant and obviously cystic. It extended from the base of the pedunculi cerebri behind, right across the base of the brain to in front of the optic chiasma. This lay flattened on the inferior aspect of the tumour, and the other structures and landmarks on this basal portion of the brain were distorted out of all recognition.

The pituitary body appeared perfectly normal in size and shape, being protected from pressure by its bony bed. The dorsum sellæ, however, and the base of the brain immediately behind this were considerably flattened, and even hollowed out to receive the tumour.

On medial sagittal section it was found that the tumour was chiefly made up of a single large cystic cavity, containing a thin serous fluid. Its walls were thick and uneven from

corrugations of the surface. These were caused by smaller cysts containing a clear homogeneous albuminous substance. The tumour had obliterated the third ventricle almost completely, this cavity being represented by a small space at the upper and posterior part, near the aqueduct of Sylvius (Figs. 1 and 2).

Coronal sections showed that the tumour had extended into the thalamus on both sides. On the left a thick layer of

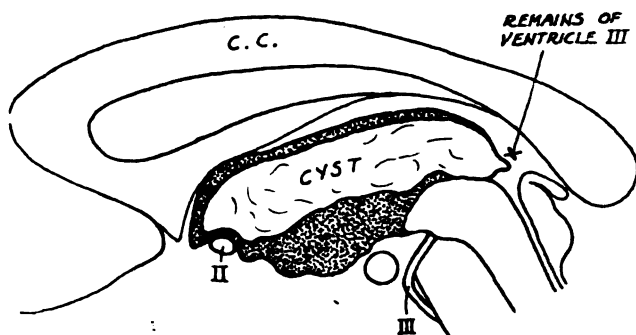


FIG. 1. Medial view of right hemisphere.

C.C., corpus callosum; II, optic tract; III, third nerve.

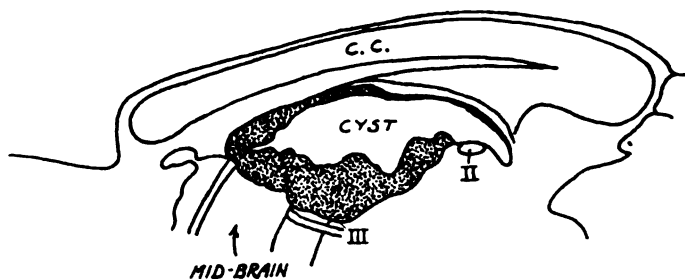


FIG. 2. Medial surface of left hemisphere.

the tumour substance with cystic degeneration had invaded this nucleus. On the right the thalamus was represented by a thin layer of grey matter on the surface of the large cyst (Figs. 3 and 4).

The lateral ventricles were slightly dilated.

#### MICROSCOPIC EXAMINATION

The pituitary body was unfortunately not kept for microscopical examination.

Section of the tumour showed that most of the cysts were lined by squamous epithelium with cells resembling those of

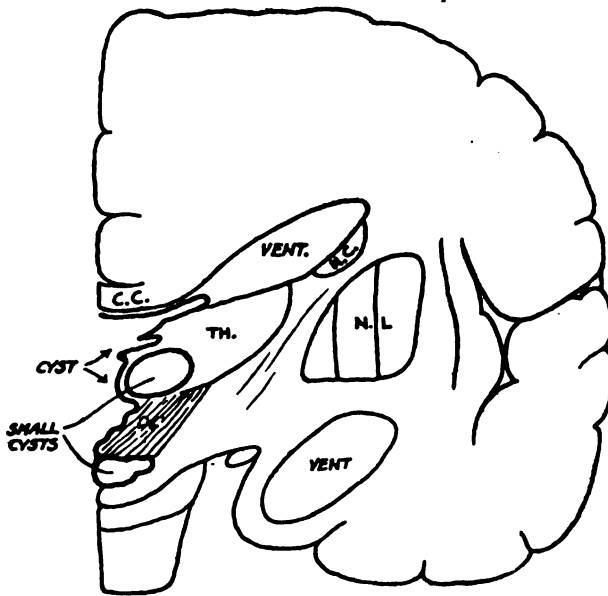


FIG. 3. Section of left hemisphere.

C.C., corpus callosum; vent., ventricle; N.C., nucleus caudatus;  
N.L., nucleus lenticularis; TH., thalamus.

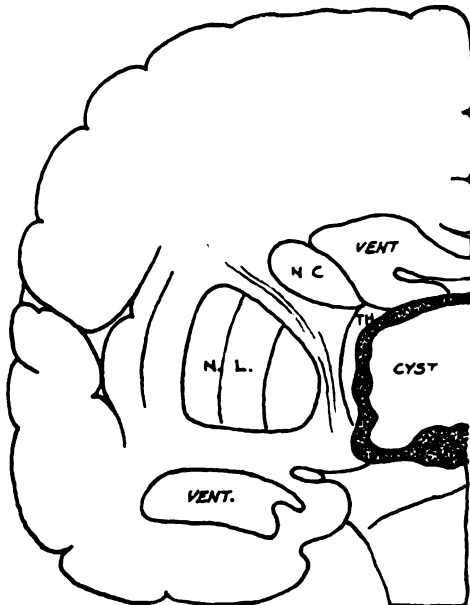


FIG. 4. Section of right hemisphere.

the rete Malpighii. Prickle cells were present, and here and there abortive attempts at keratinisation, with the formation

of small cell-pearls. This epithelium was supported on a layer of connective tissue into which it sent irregular papillary projections.

One of the cysts was lined by a layer of cubical and flattened epithelium, and was filled with delicate branching processes covered by a similar flattened epithelium.

These appearances conform with those frequently described in previous records of epithelial tumours in this situation. Two separate theories have been offered in explanation of their occurrence. The first, originally proposed by Erdheim,<sup>12</sup> presumes their origin from "cell rests," cut off from that process of the buccal ectoderm which in the embryo forms the cranio-pharyngeal duct, and which is subsequently obliterated save for its tip, which develops into the anterior lobe of the pituitary body. In support of this view Erdheim has demonstrated the presence of such "cell rests" in the neighbourhood of the pituitary body in 10 out of 13 fœtuses examined with this object. This hypothesis has been accepted by Cushing<sup>10</sup> in his pathological classification of "Pituitary Tumours." The alternative explanation is that these tumours arise from the ependymal lining of the third ventricle and its infundibular diverticulum, the metamorphosis of columnar into squamous epithelium being an instance of metaplasia.

These theories have been fully reviewed by Armstrong<sup>1</sup> with an account of the literature. Nicholson<sup>17</sup> admits the validity of both hypotheses, and the existence of epithelial tumours in this region of two kinds.

Comparing our tumour, however, with the previous records we discover features common to all, in the tendency to cystic degeneration and calcification together with a well-marked histological resemblance, and it would appear difficult to draw any sharp line of distinction between an ependymal and a cranio-pharyngeal group.

#### COMMENTS

The main interest of the case which we have reported lies in its bearing upon the still vexed problem of pituitary function. It is a matter for regret that the pituitary body was not preserved for microscopic study, but we have the evidence of Professor Stokes that it was of normal size and natural appearance. If, then, we accept the integrity of this gland (so-called) we have an instance of a case presenting during life the syndrome of Fröhlich without damage to the pituitary body, but with extensive destruction of the infundibulum and hypothalamic region.

Reports of similar cases are steadily accumulating and lead naturally to a critical review of the prevalent conception of the pituitary functions.

Cushing<sup>9</sup> and his co-workers in 1910, as the result of prolonged experimental observations, concluded that the posterior lobe or pars nervosa of the pituitary secreted, in the form of hyaline droplets, a substance which was normally discharged into the third ventricle, and that destruction of the posterior lobe, either experimental or as the result of disease, depriving the organism of this secretion, led to a group of symptoms—adiposity, high sugar tolerance, apathy, mental dulness and sexual regression—which they described as hypopituitarism.

These conclusions have been widely accepted, and are indeed plausible, suiting well with the discovery that extracts of the posterior lobe possess certain pharmacological activities.

Nevertheless, the experimental results obtained by others during the past decade, while confirming in the main Cushing's observations, have thrown some doubt upon the validity of his conclusions.

Aschner<sup>2</sup> was apparently the first to declare that by extirpation of the pituitary gland in adult dogs he was unable to produce the "hypopituitary" syndrome. His paper was shortly followed by that of Camus and Roussy,<sup>7</sup> published in 1913, leading to a series of investigations reported in several papers<sup>8</sup> and summarised in a report to the Neurological Society of Paris in 1922.<sup>6</sup>

Briefly, their contention is that the symptoms ascribed by Cushing to ablation of the pituitary were in all probability due to injury to neighbouring nerve centres in the floor of the third ventricle. These centres, comprising a group of nuclear masses in the tuber cinereum, they believe to exercise in the normal animal a control over the metabolic and sexual functions of the organism. Their destruction is responsible for derangement of these functions.

The experimental basis for these arguments may be briefly reviewed.

In the first place Cushing had concluded that the presence of at least a part of the pituitary body in dogs was essential to life. Camus and Roussy,<sup>6</sup> on the other hand, claim to have preserved alive for periods of several months animals whose pituitary bodies had been completely removed at operation. These animals were ultimately sacrificed and histological proof obtained that no pituitary substance had been left.

With regard to the polyuria which Cushing had observed after experimental removal of the gland, sometimes of a

permanent nature, and amounting to an experimentally produced diabetes insipidus, Camus and Roussy are explicit in their statement that if the pituitary had been removed without injury to the base of the brain, no polyuria resulted. On the other hand, in experiments in which the base of the brain was damaged without any lesion of the pituitary, polyuria was frequently observed.

They further showed that if after preliminary removal of the pituitary without polyuria, a lesion of the base of the brain was produced at a second operation, polyuria subsequently developed.

Their conclusion is that the polyuria obtained as a result of experimental injury of these nerve centres does not depend upon the presence of the pituitary body.

With regard to the genital functions they remark : " Removal of the pituitary body, when it is achieved without damaging the base of the brain, does not cause atrophy of the external genitals in the dog. We have often observed dogs, some months after removal of the pituitary, preserve their sexual vigour and cover bitches. Similarly, a pregnant bitch after a removal of the pituitary which at the time of operation we judged complete, gave birth 40 hours later to living pups, which she suckled for several days. On the other hand, after several experimental lesions of the base of the brain, we have observed genital atrophy in the dog, or at least arrest of development and loss of sexual appetite."

They conclude also that the obesity following operations in this region is due to a similar cause. They were unable to observe this sequel after the removal of the pituitary body unless the base of the brain were also damaged. On the other hand, an experimental lesion confined to the base of the brain frequently gave rise to a rapid increase in the body weight due to increased deposition of fat—in one dog, for instance, an increase from 19 kilos. to 26 kilos. in 3 weeks. When, as occurred in some of the experiments, this adiposity was associated with the symptoms already described, the complete Fröhlich's syndrome was present as the result of a lesion confined to the nervous substance at the base of the brain.

Bailey and Bremer <sup>4</sup> have repeated the work of Camus and Roussy, with certain improvements upon their operative technique designed to insure the pituitary body from possible damage in experimental lesion of the hypothalamic region. They employed 23 dogs in their experiments, and at the conclusion of each case subjected both the pituitary body and the nervous tissues to careful microscopic examination.

Their results confirm those of the French observers.

They found that a lesion of the para-infundibular region of the hypothalamus provoked with certainty a polyuria which, according to the extent of the lesion, varied from a transient affair (6 to 8 days) to a permanent condition of diabetes insipidus. An extensive lesion of the tuber cinereum was incompatible with life, the animals dying either immediately after operation, or, after a period of apathy, in convulsions. In two animals, however, which survived an incomplete lesion, microscopic evidence of testicular atrophy was forthcoming. And in one other instance the complete Fröhlich's syndrome developed in association with persistent polyuria. This dog was eventually killed and the pituitary body and its blood supply were proved microscopically to be intact. The nervous lesion had detached the posterior lobe from the infundibulum.

Such are the results of recent experiments upon the functions of the pituitary *in vivo*. They demonstrate, it seems clearly enough, that certain functions which have been generally attributed to the pituitary must be relegated to the brain.

The physiological action of the posterior lobe extracted *in vitro* is not disputed, but, Camus and Roussy maintain, this is another matter. That such an extract produces certain effects when injected into the body is no proof that the organ from which it was extracted normally produces similar effects.

The clinical data which support these experimental conclusions are in the first place such as are afforded by the case which we have reported, in which a tumour destroying the hypothalamic region but leaving the pituitary body intact gave rise during life to the typical Fröhlich's syndrome.

Similar instances have been recorded by Armstrong<sup>1</sup> and others.<sup>15</sup> Most valuable are those examples in which the pituitary has been demonstrated to be normal on microscopic examination, of which there are at least three upon record.<sup>13 14 19</sup>

In the second place, encephalitis lethargica has provided us with examples of Fröhlich's syndrome as a sequel of a disease which as far as we know is confined to the nervous system. Such cases are of not uncommon occurrence, and many have been reported.<sup>11 16 18</sup> So many of the symptoms of encephalitis lethargica are definitely related to lesions in the neighbourhood of the third ventricle (including probably the drowsiness) that it seems reasonable to assume that the adiposity and loss of sexual vigour are also due to damage of nervous centres in its floor. Microscopic proof of this assumption would be of great value.

Indeed, it is clear that in all cases of so-called hypopituitarism coming to autopsy a careful microscopic examination should be made not only of the pituitary body, but also of the nervous substance of the hypothalamic region. Through such investigations we may fairly hope to accumulate such clinical evidence as will go far to determine the actual functions of the normal pituitary body.

We are indebted to Dr. Herbert French, under whose care the patient was admitted, for permission to publish the case.

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# PATHOGENESIS OF GASTRIC AND DUODENAL ULCER

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## (A) THE ACUTE ORIGIN OF CHRONIC ULCERS

As histological signs of chronicity can only become obvious after an ulcer has been present for some time, it would appear natural that what are called chronic gastric and duodenal ulcers originate as acute ulcers. If this view is accepted, the pathogenesis of chronic gastric and duodenal ulcer becomes much simplified, as nearly all the experimental work has been done on acute ulcers, and it is far easier to recognise clinically the cause of an acute condition than of a chronic one, which may have been present for months or even years before it gives rise to symptoms or is discovered post-mortem.

There is no doubt that the vast majority of acute ulcers heal, but under certain conditions, which will be discussed later, they may become chronic. In addition to the acute gastric and duodenal ulcers sometimes found after death from acute infections and burns, similar ulcers are occasionally found, which show unmistakable signs of becoming chronic, especially if death has been delayed for some time after the onset of the acute event, and in a few cases acute and very early chronic ulcers have been found in the same stomach.

If an acute ulcer becomes chronic and the primary cause is not removed, more acute ulcers may develop. Consequently acute ulcers are occasionally found associated with chronic ulcers. Habershon<sup>1</sup> performed a post-mortem on a case of this kind at Guy's in 1857. Sometimes too the mucous membrane at one part of the border of a chronic ulcer undergoes acute ulceration, especially if some acute infection has occurred as an intercurrent event.

Clinical evidence can never be very conclusive, as chronic ulcers very often begin insidiously and acute ulcers give rise to no symptoms unless they erode a blood-vessel or perforate. But it is not uncommon for a patient presenting the typical picture of a case of chronic ulcer to have had one or more isolated attacks of hæmatemesis or melæna without any other symptoms, months or years before the onset of the symptoms

of which he now complains. In all probability the original hæmorrhage or hæmorrhages occurred from an acute ulcer or a succession of acute ulcers, the last of which, instead of healing, gradually developed into a chronic ulcer, which remained latent until the more recent digestive symptoms appeared.

#### (B) THE ACID FACTOR

In considering the pathogenesis of chronic gastric and duodenal ulcers, one of the most striking facts to be explained is their strictly limited localisation. They only occur in those parts of the stomach and duodenum which are habitually bathed with acid chyme, and they occur in other parts of the alimentary tract only under exceptional conditions when for any reason they are also exposed to the action of gastric juice. The one segment of the stomach in which chronic ulcers are never found is the dome-like roof of the fundus, and during the fifteen or sixteen hours of each day in which the erect position is maintained, this part can be seen with the x-rays to be separated by a collection of gas from the fluid or semi-fluid acid contents of the stomach.

Chronic duodenal ulcers are never found beyond the bulb, which is the receptacle for the acid chyme as it is evacuated from the stomach. The chyme passes so quickly through the rest of the duodenum, in which, moreover, it is very rapidly neutralised by the abundant secretion of alkaline bile and pancreatic juice as well as the duodenal juice, that the mucous membrane only occasionally and for very short periods at a time comes into contact with free hydrochloric acid.

After a gastro-enterostomy gastro-jejunal ulcers may form where the gastric and jejunal mucous membrane join, and jejunal ulcers may form opposite the stoma and in the three or four inches of jejunum distal to the stoma. Gastro-enterostomy sometimes leads to the complete disappearance of free acid from the gastric contents throughout a fractional test-meal. In other cases, however, and especially if the operation has been performed for a duodenal ulcer, free acid is still present, and the lips of the stoma and the first few inches of the jejunum distal to the stoma are exposed to strongly acid chyme. It is only in the latter group of cases that gastro-jejunal and jejunal ulcers occur. I have never seen a case in which free acid was not present, often in considerable amount. No acid chyme reaches the proximal loop of the jejunum, and that which enters the distal loop is completely neutralised by the alkaline fluids coming from the duodenum before it has passed more than three or four inches, beyond which jejunal ulcers never develop.

Ulcers of the kind found in the stomach and duodenum do not occur in other parts of the small intestine with the exception of those already mentioned as following gastro-enterostomy, and they do not bear the slightest resemblance to any of the various forms of ulcer of the colon.

In a small proportion of cases of chronic gastric ulcer, but so far as my experience goes never in chronic duodenal ulcer or acute gastric or duodenal ulcer, complete achlorhydria is found throughout a fractional test-meal. There is generally a long history of indigestion and the ulcer is generally a large and very chronic one. It is very improbable that achlorhydria has always been present in such cases; it is more likely to be secondary to the chronic gastritis with which gastric ulcers of this kind are often associated. In some cases a normal curve of acidity is obtained if the stomach is thoroughly washed out before the test-meal, the free acid having apparently been completely neutralised by the excess of mucus present when the first meal was taken. In any case the quantity of organically and inorganically combined hydrochloric acid found shows that true achylia, in which there is a congenital or acquired absence of gastric secretion, such as is present in most cases of Addison's anæmia, is not present, but that the hydrochloric acid, which is secreted in normal or, more often, in less than normal amount, is completely neutralised by the organic and inorganic alkaline substances present in the stomach. Rüttimeyer<sup>2</sup> has shown that the pepsin is present in normal quantity in these cases, and that there is always sufficient organically combined acid present to activate it, so that the gastric contents are still capable of exerting a digestive action on a chronic ulcer.

Experimental evidence, so far as it goes, entirely confirms the clinical evidence that the presence of acid in the gastric contents is an essential factor in the development of ulcers. Bolton<sup>3</sup> succeeded in producing acute gastric ulcers in animals by a gastrototoxic serum, prepared by repeatedly inoculating a different species of animal with an emulsion or saline extract of the gastric mucous membrane of the same kind of animal as that for which the serum was to be used. He found that complete neutralisation of the gastric contents with sodium bicarbonate not only prevented the development of the acute ulcers, but also of the localised areas of necrosis, which formed the first stage in their production. On the other hand, increasing the acidity of the gastric contents by the administration of hydrochloric acid hastened the formation of the ulcers. Although no poison analogous to Bolton's gastrot toxin occurs in human pathology, the ulcers it produces are anatomically indistinguishable from

the acute ulcers produced by bacterial toxins in man. The presence of free hydrochloric acid is therefore in all probability just as essential for the formation of the latter as for the formation of the experimental ulcers in animals. The toxin may be sufficiently powerful to produce the primary area of necrosis by itself, or it may resemble Bolton's gastrot toxin in only impairing the vitality of the stomach cells, so that the additional destructive action of hydrochloric acid is required in order to produce actual necrosis. In both cases the formation of an acute ulcer depends upon the digestion of the necrotic tissue by the pepsin of the gastric juice, which cannot act in the absence of free or organically combined hydrochloric acid.

From what has been already said it is obvious that the old term of peptic ulcer is quite appropriate, and it has the advantage of including gastric, duodenal, gastro-jejunal and jejunal ulcers all under a single generic name corresponding to their common pathogenesis.

We have seen that the presence of hydrochloric acid is an essential factor in the formation of gastric and duodenal ulcer. It may lead to their extension when once formed, though it is clearly not the only factor, or acute ulcers would not show such a remarkable tendency to heal, both extension in area and in depth being quite exceptional events. Much more often it is one of the factors which result in an acute ulcer becoming chronic instead of healing, but here again, though an essential factor, it is never the only one, as many more acute ulcers heal than become chronic. Lastly it is an important factor in preventing chronic ulcers from healing. This is recognised in both medical and surgical treatment. The most suitable diet is one which leads to a minimal secretion of gastric juice and contains a maximum of substances which can neutralise some of the acid secreted, and drugs are given with the same objects of inhibiting secretion and of neutralising as much as possible of the acid as is secreted.

Though surgical treatment, especially of gastric ulcers, is largely directed to the radical removal of the ulcer and ulcer-bearing area, in many cases, especially of duodenal ulcer, only indirect treatment is possible, and this depends for its success to a large extent upon its influence in diverting the acid chyme from the ulcer and in neutralising it whilst still in the stomach. Whatever its other disadvantages and dangers, gastro-enterostomy is an ideal operation for duodenal ulcer in so far as the acid factor is concerned, as in successful cases all of the acid chyme passes through the stoma, so that the ulcer, being no longer exposed to the digestive action of the gastric juice, almost

always heals with great rapidity. On the other hand, the operation is far less satisfactory in cases of gastric ulcer, though the more rapid evacuation of the stomach and the partial or even complete neutralisation of the gastric contents by the alkaline fluids, which enter the stomach through the stoma from the proximal loop of the jejunum, deal more or less effectively with the acid factor, because other factors than acid are of much greater relative importance than in the case of duodenal ulcer.

### (C) THE INFECTIVE FACTOR

Acute ulcers of the stomach are occasionally found after death from acute septic infections, such as septicæmia, pyæmia, infective endocarditis, and septic forms of scarlet fever and small-pox. They may also occur with acute localised septic processes, the most important of which is septic peritonitis from various causes, especially appendicitis. Other conditions which are sometimes, though less frequently, associated with acute ulcers are suppurative cholecystitis, strangulated hernia and suppurative salpingitis, empyema, broncho-pneumonia, chronic phthisis with infected cavities, bronchiectasis, abscess of the lung, and antral empyema, pyelonephritis, cellulitis and erysipelas. In only a small proportion of these cases is the ulcer the cause of death. Thus death only resulted from the ulcer in two out of fifty-three cases in which an acute ulcer was found in a consecutive series of 1500 autopsies performed at Leeds by Stewart<sup>4</sup>; in one, a man of 42, death was due to mesogastric and mediastinal cellulitis following these acute ulcers near the cardia, and in the other, an infant of four months, death followed hæmorrhage from multiple acute duodenal ulcers.

A man was admitted under my care at Guy's some years ago with anthrax. The malignant pustule was excised and 40 c.cm. of anti-anthrax serum were injected subcutaneously. About six hours later he experienced a sense of heaviness in the abdomen and then vomited about a pint of blood. He was given an injection of morphia, but his diet was not altered. He made a satisfactory recovery and there were no further hæmorrhages or other gastric symptoms.

In some of these conditions bacteria have been found in the floor or edges of the ulcers, in thrombi lodged in neighbouring vessels, and in lymphatics, but in others the ulcers have been sterile, and in any case the bacteria found in connection with the ulcers are not necessarily the same as those responsible for the primary disease. It is clear that the gastric lesion is caused by bacterial toxins. These may be produced locally by

organisms situated in the small vessels of the gastric mucous membrane, to which they have been conveyed by the blood stream, or they may be produced in the primary seat of the disease, from which they are carried by the blood to be excreted by the gastric mucous membrane. Thus I have seen very severe hæmatemesis occur in a woman who was receiving streptococcal vaccines for rheumatoid arthritis; as no gastric symptoms had been present before and none occurred during the three following years, it is probable that the hæmorrhage took place from an acute ulcer. That non-bacterial toxins can act in the same way is shown by the occurrence of acute ulcers, especially of the duodenum, after burns, which are not necessarily septic.

Numerous experimental investigations have given results which strictly correspond with these clinical observations. Since acute ulcers were first produced in animals by the injection of a culture of *Staphylococcus aureus* by Letulle<sup>5</sup> in 1888 and of diphtheria toxin by Enriquez and Hallion<sup>6</sup> in 1898, many observers have produced similar ulcers with a great variety of bacteria and bacterial toxins.

As the toxæmia of acute infections can undoubtedly give rise to acute ulcers of the stomach and duodenum, though, according to Stewart, it only accounts for about one-half of the cases in which the latter are found after death, it would not be surprising if the toxæmia of chronic infections had the same effect, as the toxins would act for a longer period, although in a less concentrated form. The clinical evidence for this is not absolutely conclusive, as chronic infections are so common that the possibility of coincidence requires consideration. But the association of chronic appendicitis with acute ulcers is too common to be explained by coincidence, and the causal connection is made still more probable by the frequency with which repeated hæmatemesis from recurrent acute ulcers ceases after the removal of an inflamed appendix. As chronic ulcers probably always originate as acute ulcers, the well-recognised connection between chronic appendicitis and chronic ulcer, especially of the duodenum, is doubtless of the same nature.

I have seen several cases of acute ulcer associated with chronic tonsillar infection, and I have never failed to find some other source of infection, generally in the teeth, in those cases of hæmatemesis from acute ulcers, in which neither the appendix nor the tonsils were diseased. The infection from tonsils and teeth might theoretically be either from swallowed bacteria, which invade the gastric mucous membrane, or from bacteria or their toxins which reach the mucous membrane by way of the blood-stream. In the large majority of cases the infection

is undoubtedly hæmatogenous, though when an ulcer has once formed, secondary infection of its exposed surface by swallowed bacteria may of course occur. Knott <sup>7</sup> has, however, shown that even the smallest quantity of free hydrochloric acid very rapidly destroys streptococci, so that unless gastric secretion is deficient or absent, swallowed bacteria originating in the tonsils or from pyorrhœa alveolaris are likely to be destroyed before they can invade an ulcer. But in achylia gastrica, in which such invasion might occur, acute ulcers are probably never present, as the free acid of the gastric contents is an essential factor in their development. Thus no case of Addison's anæmia, in which achlorhydria is always present, has ever been recorded, in which an acute or chronic ulcer was found post-mortem, although septic complications are not uncommon as terminal events. It is only in chronic gastric ulcers associated with hypochlorhydria or even achlorhydria that such secondary infection is likely to be of much importance.

Bacteria and their toxins can pass from the deeper tissues of the periodontal ulcers of pyorrhœa alveolaris into the bloodstream and also from infected roots. The latter condition is all the more important clinically, as it may be associated with perfectly normal-looking teeth and can only be recognised with the aid of the x-rays.

Rosenow, <sup>8</sup> formerly of Chicago and now of the Mayo Clinic, has carried out an extensive series of investigations, which throw a flood of light on the infective origin of gastric and duodenal ulcers. As long ago as 1874 Böttcher <sup>9</sup> had demonstrated the presence of bacteria in the edges and floors of ulcers, and more recently Dudgeon and Sargent <sup>10</sup> isolated a diplostreptococcus from the edges of the ulcers in four out of nine cases of peritonitis following perforation. Rosenow has isolated streptococci from the deep tissues of forty-two out of fifty-four chronic gastric and duodenal ulcers excised during life, after freeing them from surface contamination, and four out of five times from neighbouring lymphatic glands. The largest number of bacteria were found in the most acute ulcers, and none were present in those which showed signs of healing. Other bacteria were sometimes found, but always in smaller numbers. Their causal connection with the ulcers was proved by the fact that they were to some extent specific, as the intravenous inoculation of their cultures into animals produced gastric and duodenal ulcers in a very much larger proportion of cases than when the streptococci used were obtained from various foci of infection in patients not suffering from ulcer. The ulcers resembled those found in man in their localisation, macroscopic

and microscopic appearance, and in their tendency to become chronic, to perforate and to cause serious and sometimes fatal hæmorrhages.

More recently Rosenow has obtained the same results with dead bacteria and with filtrates of active cultures, showing that the bacterial toxins are also effective, though the lesions were less severe, and, as no bacteria were present to produce more toxin, healing occurred more rapidly.

On immunising rabbits with the specific streptococcus, but not with streptococci obtained from other sources, the liability to the formation of ulcers was greatly reduced—from 82 to 17 per cent.

The relative affinity of the streptococci for the stomach and duodenum disappeared after cultivation for one to six weeks on artificial media, and also after animal passage, but on keeping the organisms in "latent life" under relatively anaërobic conditions their specific properties might be preserved for as long as eight years. Rosenow also found that streptococci isolated from infected teeth and infected tonsils of patients with gastric and duodenal ulcer frequently produced ulcers in animals, but those isolated from similar teeth and tonsils of patients suffering from some other disease, or with nothing else the matter than the local infection, only produced gastric and duodenal ulcers in a very small proportion of animals. Some observers have failed to confirm his work, but, according to Rosenow, this is due to the fact that they have not employed the technique which, after numerous experiments, he found was required in order to obtain positive results.

These investigations show that the teeth and tonsils may be infected with streptococci, the toxins of which have a specifically destructive effect on the gastric and duodenal mucous membrane. If some of the streptococci pass into the bloodstream from the infected teeth and tonsils and produce an area of sub-infection in the mucous membrane of the stomach or duodenum, toxins are produced locally, which devitalise the tissue, so that it is digested by the gastric juice and an acute ulcer forms. Under favourable conditions this rapidly heals, but new acute ulcers continue to develop so long as the sub-infection can be renewed from the primary focus of infection in the teeth or tonsils. Under certain circumstances the healing process is prevented and a chronic ulcer develops, which is likely to remain active unless the primary foci are eradicated.

#### (D) THE PROCESS WHICH PRECEDES ULCERATION

There have been many theories propounded to explain why the gastric juice does not normally digest the mucous membrane



of the stomach, but it is now generally believed that the absence of auto-digestion is due to the presence, discovered by Weinland,<sup>11</sup> of an antipepsin in the gastric mucous membrane.

Studies in the morbid anatomy of acute ulcers in man and the very numerous experimental investigations on the production of acute ulcers in animals show that a portion of the gastric or duodenal mucous membrane must be more or less devitalised before the gastric juice can digest it and produce an ulcer.

Acute ulcers in man are sometimes associated with minute areas of necrosis, and much less frequently with minute areas of hæmorrhage, which are more often found in the same stomachs as necrotic areas. In other cases the process is incomplete and part of the necrotic tissue is still present in one part of the acute ulcer. The pathological changes may take place with remarkable rapidity, as shown by the fact that an acute ulcer has been found in the duodenum as early as nineteen hours after death from a severe burn. By killing animals at various intervals after an ulcer-producing toxin has been injected, the different stages of their formation can be traced. It has been conclusively proved that an area of necrosis forms first, and that the necrotic tissue is then digested by the gastric juice with the production of an acute ulcer.

Bolton<sup>3</sup> has shown that the toxin itself does not necessarily produce actual necrosis, but that if it devitalises the tissue sufficiently, the process can be completed by the toxic action of the hydrochloric acid of the gastric juice or by other irritants, such, for example, as vinegar, all of which are quite harmless themselves, unless the preliminary damage has been done by the injected toxin. Bolton's experiments were carried out with his gastrotoxin, but bacterial toxins probably act in a similar manner. He found that if the gastric juice was neutralised the injection of gastrotoxin had no obvious effect, so that it was clear that the toxin by itself produced nothing more than a recoverable injury to a small area of the mucous membrane, and that the toxic effect of the acid of the gastric juice was required to produce the necrosis. Finally, the pepsin of the gastric juice, activated by the hydrochloric acid, digested the necrotic tissue and produced the ulcer.

These observations explain the clinically observed fact that the habitual consumption of chemical irritants, such as vinegar and alcohol, appears to increase the liability to ulcer, and, what is perhaps still more commonly observed, predispose to recurrences after ulcers have healed.

In Rosenow's experiments on the production of ulcers in animals by the injection of streptococci isolated from chronic

ulcers in man, the bacteria were found to lodge in the fine capillary network round the gland tubules or in tissue spaces, and then to multiply with great rapidity; this was followed by hæmorrhage and necrosis, or necrosis alone, after which the overlying mucous membrane sloughed and carried away with it most of the bacteria, leaving in its place a typical acute ulcer. Perhaps similar areas of devitalised tissue are produced by the toxins in the intestine as well as the stomach, but whereas in the intestine healing rapidly occurs, in the stomach and the duodenal bulb the tissue is digested by the gastric juice and a minute ulcer develops.

Reeves<sup>12</sup> has shown that the circulation in the vessels of the submucous arterial plexus on the lesser curvature tends to be slow compared with that in other parts of the stomach owing to their much smaller size, their greater length and the few anastomoses they make. When the stomach is full all of the rugæ of the mucous membrane disappear except an anterior and a posterior fold, which run along the lesser curvature from the cardia to the pylorus. The arteries, which are spiral and very tortuous when the stomach is empty, straighten out, with the result, as Waldeyer first pointed out, that the resistance to the blood-stream is reduced and a free flow to the mucous membrane is assured, quite apart from the active dilatation which depends upon vasomotor changes occurring during digestion. But, as the two folds along the lesser curvature remain unaltered, the arteries of the lesser curvature, which even in the contracted stomach offer a greater resistance to the blood flow than elsewhere, show a still more striking difference in the distended stomach, as they alone retain their spiral and tortuous character.

Reeves has also found that the submucous plexus of arteries in the duodenal bulb is made up of vessels, which are few in number and small, and do not anastomose freely when compared with those of other parts of the duodenum.

These anatomical peculiarities of the arteries of the lesser curvature of the stomach and the duodenal bulb help to explain why ulcers are more likely to form in these parts than in the rest of the stomach, as the circulation is slower and the lumen of the vessels is smaller, so that infective emboli can lodge in them and thrombosis can occur in them more readily than elsewhere.

#### (E) INFECTION OF THE LYMPHOID TISSUE IN THE GASTRIC MUCOUS MEMBRANE

Minute lymphoid follicles are present in the gastric mucous membrane at the base of the glandular crypts and superficial

to the muscularis mucosæ. They are more numerous and larger in the pyloric vestibule than in the cardiac part of the stomach, and near the lesser curvature than near the greater curvature. They are also very numerous in the duodenal bulb. Cruveilhier was the first to suggest that gastric ulcers might arise from rupture into the lumen of the stomach of abscesses developing as a result of inflammation of these follicles. In Carswell's *Atlas of Pathological Anatomy*, published in 1838, there is a drawing of a stomach with enlarged lymphoid follicles, some of which have formed abscesses, which have in two places ruptured to produce minute follicular ulcers.

The "weeping" but not obviously ulcerated mucous membrane first described by surgeons twenty years ago, when operations were more frequently performed for hæmatemesis than they are to-day, was probably a result of acute gastritis, in which the lymphoid follicles had become inflamed; many had suppurated and ruptured into the stomach at the same time as eroding the smallest blood-vessels. The inflamed mucous membrane was swollen and so prevented the minute apertures into the abscesses from being seen, but merely touching the mucous membrane was sufficient to cause further oozing of blood. In the very small number of cases which were satisfactorily investigated post-mortem the explanation just given was shown to be correct.

It seems probable that the lymphoid follicles are infected by swallowed bacteria rather than by bacteria reaching the mucous membrane by the blood-stream. Thus Turck<sup>13</sup> fed animals for two to four months on daily doses of 50 to 1000 c.cm. of culture of *B. coli* mixed with meat. The lymphoid follicles of the stomach invariably became infected, and minute gastric or duodenal ulcers developed. Acute ulcers produced by hæmatogenous infection, on the other hand, are of the usual form which begins with necrosis, and the lymphoid follicles are not involved.

It has been suggested that chronic gastric ulcers may develop from these acute follicular ulcers, but there is no evidence for this, and it is much more probable that they are always a sequel of the acute ulcers produced by hæmatogenous infection or intoxication.

#### (F) PREDISPOSING CAUSES: THE ULCER DIATHESIS

I have discussed the duodenal ulcer diathesis in considerable detail elsewhere, so<sup>14</sup> will here only summarise my views on the subject. The recent investigations of Campbell and Conybeare<sup>15</sup> have shown that a large proportion of healthy

men with hyperchlorhydria have also hypertonic stomachs. These are the individuals who possess what I have called the hypersthenic gastric diathesis, an inborn variation from the average normal, which manifests itself in hypertonus with active peristalsis and rapid evacuation, and in hyperchlorhydria with digestive hypersecretion. This condition, though compatible with perfect health, is, I believe, the essential predisposing factor in the production of duodenal ulcer. It is, like duodenal ulcer, much more common in men than in women, and is often present in several members of the same family.<sup>16</sup> In the average normal man undiluted gastric juice rarely enters the duodenum, and when it does its acidity is low, but in people with the hypersthenic gastric diathesis undiluted juice of considerable acidity leaves the stomach for several hours out of each twenty-four. The anatomy and physiology of the duodenum are such that during the whole of this time the bulb, but no other part of the duodenum, is continually in contact with this undiluted and exceptionally acid juice, the bulb being also the only part in which ulcers develop. If infection or intoxication, the essential exciting factors of ulceration, is also present, an ulcer will form in the duodenal bulb.

The results of Rosenow's investigations on the specific properties of the streptococci isolated from gastric and duodenal ulcers explain the important part played by dental and tonsillar infection in the production of ulcers, but they do not explain why gastric ulcers occur in some cases and duodenal ulcers in others. Thus the specificity of the infection is for ulcer in general, and not as a rule for gastric or duodenal ulcer in particular, as it is exceptional for the relative frequency of the experimental production of lesions in the stomach and in the duodenum to vary according to the situation of the ulcer in the patient from whose teeth, tonsils, or ulcer the streptococci were isolated.

Gastric or duodenal lesions developed in 9 per cent. of animals inoculated with streptococci from the infected teeth or tonsils of individuals otherwise healthy, or suffering from diseases other than ulcer, cholecystitis or appendicitis. They also developed in 11 per cent. of animals inoculated with streptococci from cases of appendicitis, and in 29 per cent. from cases of cholecystitis. As none of these patients had a gastric or duodenal ulcer, it may be assumed that they differed from those patients with gastric or duodenal ulcer in whom similar streptococci were isolated in being constitutionally less liable to develop chronic ulcers. Thus in most people the minute areas of necrosis in the gastric or duodenal mucous membrane, which are caused by hæmato-

genous infection conveyed from the teeth, tonsils, appendix or elsewhere, rapidly disappear under ordinary conditions; either no symptoms occur at all, or acute ulcers develop, which quickly heal, though they may occasionally give rise to hæmatemesis or even perforation. But in the presence of the peculiar condition which I have described as characteristic of the hypersthenic gastric diathesis, a minute area of necrosis in the duodenal mucous membrane is unlikely to heal. It will be digested by the acid gastric juice, with which it is in contact for several hours during the day and intermittently during the greater part of the night. Not only will healing fail to occur, but a chronic ulcer may develop.

It is much less easy to define what are the predisposing causes of gastric ulcer—what, in fact, constitutes the gastric ulcer diathesis. Uncomplicated gastric ulcers are rarely associated with hyperchlorhydria and never with hypertonus. The gastric acidity varies greatly in different cases. But in a considerable majority the muscular tone is somewhat deficient and more or less ptosis is present. In an individual with a hypotonic and dropped stomach the condition I have described as orthostatic hour-glass stomach<sup>17</sup> is observed, a condition in which the middle of the stomach forms a definite obstruction to the onward passage of food so long as the erect posture is maintained. This results in the mucous membrane being subjected to an abnormal amount of friction, especially on the lesser curvature, where the vast majority of gastric ulcers develop. Moody, van Nuys and Chamberlain<sup>18</sup> examined 600 healthy young adults with the x-rays, men and women being in equal numbers. They found that the average position of the greater curvature when standing was 2·5 c.m. and 4·5 c.m. below the interiliac line in men and women respectively. Whereas a hypertonic stomach was found in 17 per cent. of men and only 7 per cent. of women, a hypotonic stomach was found in 3·6 per cent. of men and 15 per cent. of women. As a hypertonic stomach is associated with duodenal ulcer and a hypotonic dropped stomach is associated with lesser curvature ulcers, these figures explain in part the relative frequency of duodenal ulcer in men and of lesser curvature ulcer in women.

It is not merely the motor and secretory functions of the stomach which differentiate individuals with the hypersthenic gastric diathesis from those with atonic dropped stomachs. Thus Campbell, writing with Conybeare<sup>15</sup> and with Baird and Hern,<sup>19</sup> found that a high hypertonic stomach with hyperchlorhydria occurs particularly in men of an athletic type with relatively short, broad chests, whereas a low hypotonic stomach

with hypochlorhydria occurs especially in men of a less vigorous type with relatively long, narrow chests.

On examining the blood of fifty consecutive patients with gastric or duodenal ulcer, in all of whom the diagnosis was confirmed at operation, and in whom visible hæmatemesis or melæna had not occurred, Friedman <sup>20</sup> found that the average hæmoglobin percentage was 75 in the cases of gastric ulcer compared with 90 in the cases of duodenal ulcer, the individual variations being between 55 and 110 compared with 65 and 120. This, again, is probably due to the constitutional difference between individuals who are subject to gastric and to duodenal ulcer respectively.

### (G) ACCESSORY FACTORS

#### (i) *Tobacco*

We have long been struck by the importance of excessive smoking in connection with duodenal ulcer. Its influence in gastric ulcer seems to be much less marked. Careful inquiry shows that a large majority of patients with duodenal ulcer have smoked excessively for years. It is difficult to say exactly what constitutes excessive smoking, but in most cases the patient knows that he smokes considerably more than the majority of his friends. In some cases a man will hardly be without a cigarette in his mouth from the time he wakes in the morning to the time he falls asleep at night, and he may not even stop smoking during meals. Excessive cigarette smoking is more common than excessive pipe or cigar smoking, but all three are common in cases of duodenal ulcer. I think one of the reasons why men have duodenal ulcers so much more frequently than women is because it is rare to find a woman who smokes excessively in the sense that a man is said to smoke excessively. It does not appear that inhaling is essential in order that smoking should aggravate a duodenal ulcer. Probably a good deal of the poison is swallowed.

Nicotine was shown by Langley <sup>21</sup> to paralyse the synapses of the sympathetic nervous system. Excessive smoking leads to the inhalation and swallowing of nicotine. Though the quantity absorbed in a day may be negligible, in course of time the poison appears to accumulate in sufficient quantity to have this effect on the synapses of the abdominal sympathetic system. The result is that the fibres, which inhibit the secretion of gastric juice and reduce the tone and inhibit the peristalsis of the stomach, are partially paralysed. The vagal nerve supply is consequently uncontrolled, so that the tendency to hyper-

chlorhydria, hypertonus and hyperperistalsis already present in people with the hypersthenic gastric diathesis is exaggerated.

By experiments carried out on himself, R. D. Roberts has shown that the curve obtained with a fractional test-meal is slightly higher during a period of excessive smoking than during a period of abstinence. In all probability the effect would have been much more obvious if the experiment had been carried out on an individual with the hypersthenic gastric diathesis, as drugs which affect the autonomic nervous system appear specially to influence any part which is already over-acting. Thus a dose of adrenalin, which is quite insufficient to raise the blood-pressure, accelerate the pulse or have any other effect on a normal individual, is sufficient to stimulate the sympathetic broncho-dilator fibres, when the vagal nerve supply to the bronchi is over-active and giving rise to the spasm and hypersecretion which constitute an attack of asthma. Similarly a dose of nicotine, which is just short of producing any obvious effect on an average normal man, will influence the gastric functions of a man with constitutional gastric hypertonus, and the intestinal functions of another with intestinal hypertonus. The liability to develop a duodenal ulcer is thus increased by excessive smoking, and when an ulcer has formed its tendency to heal is reduced and its tendency to cause pain is exaggerated. Nearly every patient is aware that his symptoms are aggravated by smoking, and many reduce their consumption of tobacco on their own initiative. A return of pain in a quiescent ulcer, or a relapse after an ulcer has healed, may follow a period of excessive smoking, and one reason why worry aggravates the symptoms of ulcer is that it is so often an excuse for over-indulgence in tobacco.

(ii) *Mental and Physical Fatigue : Suprarenal Exhaustion*

The first appearance of symptoms of duodenal ulcer often follows a period of combined physical and mental over-work, especially if it has been accompanied by worry. Still more frequently relapses and recurrences appear to be precipitated in this way. Gastric ulcer, on the other hand, does not seem to be in any way associated with over-work. The importance of the worry factor is seen in the relatively great frequency of duodenal, but not gastric, ulcer in men whose profession entails much worry as well as hard work.

The most probable explanation is that the exhaustion resulting from physical and mental fatigue exaggerates the gastric vagal hyperactivity of the diathesis which predisposes to duodenal ulcer. It seems not unlikely that it acts through the

suprarenal glands, which have been shown by the work of Crile to become exhausted and to produce less adrenalin as a result of physical and mental strain. This causes the continuous inhibitory activity of the sympathetic nervous system to be damped down. The first place in which this manifests itself is likely to be in any organ in which vagal activity tends to be excessive. Thus a man with an irritable bronchial nervous system will be likely to develop asthma, and one with a hypersthenic stomach will be likely to develop still greater motor and secretory activity with increased liability to duodenal ulceration.

A further analogy between asthma and duodenal ulcer is shown by the tendency for the symptoms to be worst at night after the evening meal, when the fatigue of the day has caused the already partly exhausted suprarenal glands to be still less active, and so to reduce the sympathetic control of the over-active vagus.

### (iii) *Food*

So many people always bolt their food and take no care about their diet without suffering from indigestion, that much stress cannot be laid on a history of habits of this kind in patients with gastric and duodenal ulcer. But it is not improbable that, when the conditions are present which are likely to lead to the development of an ulcer, the nature of the food and the time and manner in which it is eaten play a subsidiary rôle or are even the determining factors, which cause an acute ulcer to become chronic, and prevent the natural tendency for even a chronic ulcer in its early stages to heal spontaneously. Thus most patients with a gastric ulcer discover for themselves the advantages of a very plain diet, whilst those suffering from a duodenal ulcer know that, although a big and indigestible meal may postpone the onset of pain, when it does occur it is likely to be all the more severe. Moreover, all successful systems of medical treatment have for one of their principal objects the provision of an unirritating diet, and one of the essential parts in the prevention of recurrence after both medical and surgical treatment is the instruction of the patient as to what he should eat, how he should eat, and when he should eat.

Mastication has the object of bringing the food into as unirritating a chemical and physical state as possible. Large pieces of food are broken up by chewing, and most hard fragments are softened by the saliva and coated with a layer of protective mucus, though such articles as the pips and skins of fruit and the fibres of raw vegetables, such as celery, remain to a great extent unaffected. Chemical irritants, such as alcohol



and vinegar, are diluted, and very cold and very hot fluids and solids are brought nearer to the body temperature. If the teeth are good and mastication is thorough, the food should contain very little that could irritate the gastric mucous membrane mechanically, chemically, or thermally by the time it is swallowed. If, however, the teeth are insufficient in number, or the dentures which have replaced some or all of them are ill-fitting, or if the food is bolted and fluids are rapidly swallowed without being kept in the mouth at all, the stomach has to do the work which the mouth has failed to perform.

One of the chief functions of the stomach is to protect the intestine by not allowing anything to pass through the pylorus until it has lost as far as possible its irritating properties. But in the act of doing this it may itself become injured. Thus food which has not been properly broken up by mastication is vigorously rubbed against the mucous membrane of the pyloric vestibule by the churning movements which result from the peristalsis, as the pyloric sphincter only relaxes completely when the chyme, which reaches the entrance to the pyloric canal, has been reduced to a fluid or semi-fluid consistence. At the end of digestion, when the soft part of the chyme has been evacuated, lumps and hard particles of food, which the churning and rubbing in the pyloric vestibule have failed to subdivide more completely, are pushed through the pyloric canal, whilst the pyloric sphincter remains unrelaxed or is only partially relaxed.

When the stomach is of the orthostatic hour-glass form already referred to, or when, as Barclay<sup>22</sup> was the first to point out, a spasmodic hour-glass contraction is present as the result of a reflex from a diseased appendix or some other extra-gastric disease, the mucous membrane in the centre of the stomach is subjected to friction in a similar manner if the food has not been properly prepared in the mouth. This occurs especially on the lesser curvature, which is much less movable than the greater curvature owing to the tension of the lesser omentum when the patient is in the erect posture. On the other hand, the mucous membrane of the fundus of the stomach and the duodenal bulb, in neither of which any churning movements occur, remains unaffected. The duodenal bulb is also protected by the pyloric sphincter, the pyloric vestibule having done much of the work of preparation which should have been done in the mouth, so that insufficiently chewed food is broken up and hard particles are softened by the time the duodenum is reached.

When chemical irritants, the most important of which is alcohol, are taken with a meal or after a meal, they are generally

so diluted in the stomach that they cannot greatly damage the mucous membrane unless drunk in considerable quantities. If, however, alcohol is taken as a cocktail or *apéritif* before meals, or in the form of spirits between meals, when the stomach contains comparatively little chyme, it acts as an irritant to the mucous membrane. This is particularly likely to occur in the rapidly emptying stomach which predisposes to duodenal ulcer, as whisky drunk at midday, in the late afternoon or on going to bed, and cocktails and other drinks taken just before meals are not likely to be diluted at all, as such stomachs are then generally empty. The alcohol passes rapidly through the pyloric canal and consequently irritates the mucous membrane of the duodenum as well as that of the stomach. Excess of curry, mustard, pepper and vinegar taken with meals, and the acid of unripe fruit taken on an empty stomach, may sometimes act in a similar way to alcohol. In France the effect of absinthe has also to be considered, as Hayem<sup>23</sup> found erosions and small foci of necrotic tissue in the mucous membrane of the stomachs of absinthe drinkers.

W. Mayo<sup>24</sup> has often emphasised the importance of the thermal irritation produced by drinking very hot or very cold fluids in the production of gastric and duodenal ulcer. Although it is true that ices and very hot drinks are sometimes swallowed quickly in order to avoid the pain they would cause if kept longer in the mouth, the stomach being completely insensitive to thermal stimuli, I do not think that this can be of any importance except in America, which is the only country where iced water is drunk in large quantities at all times of the day. Ices are generally taken when the stomach is full, so that even if they are not allowed to melt in the mouth they cannot produce any appreciable cooling effect on the gastric mucous membrane. Hot drinks are also generally taken with meals, and most people are careful not to drink them at a temperature which will burn the mouth or cause pain in the lower end of the œsophagus, and it is very unlikely that they could exert any injurious influence under such conditions.

From what has been said it appears not improbable that the bolting of meals and the consumption of food containing hard particles, which cannot be softened by saliva or gastric juice, may be important factors in causing an acute ulcer to become chronic and in preventing a chronic ulcer from healing if the ulcer is situated in the pyloric vestibule, or in the middle of the lesser curvature in individuals with an orthostatic or spasmodic hour-glass stomach, but that it is of little or no importance in duodenal ulcer. On the other hand, strong alcohol is more

often a factor in duodenal ulcer than gastric ulcer, as it is unlikely ever to be sufficiently concentrated to cause any irritation except in individuals with the hypersthenic gastric diathesis. Lastly, thermal irritation does not appear to be of any importance, at any rate in Great Britain.

It has always been a mystery why chronic gastric ulcers should show a definite tendency to become malignant, whereas chronic duodenal ulcers, though their morbid anatomy and the factors which lead to their development are so similar, very rarely, if ever, become malignant. It seems not unlikely that the mechanical irritation to which gastric ulcers, but not duodenal ulcers, are constantly subjected is the explanation of this remarkable difference.

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## DIVERTICULA OF THE STOMACH

### A POSSIBLE SOURCE OF ERROR IN THE RADIOLOGICAL DIAGNOSIS OF GASTRIC ULCER

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TRUE diverticula of the stomach are very rare. There is a specimen in the Guy's Museum from a woman of 56, who died of phlegmonous laryngitis in 1847 (Fig. 1). They have also been found post-mortem by Zahn,<sup>1</sup> Thorel,<sup>2</sup> Handtmann<sup>3</sup> and Åkerlund.<sup>4</sup> They are invariably situated in the immediate

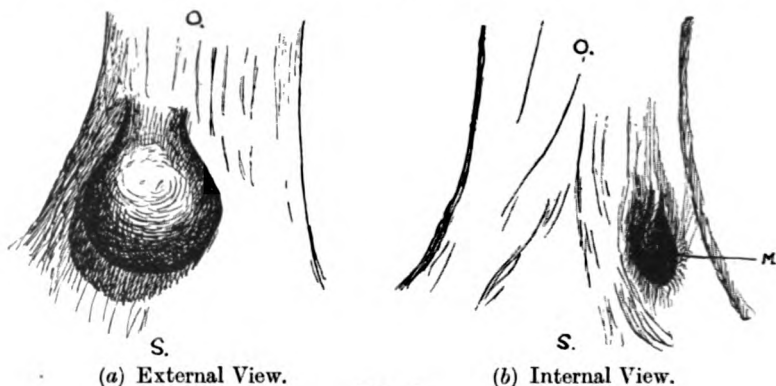


FIG. 1.

Diverticulum of stomach in Guy's Hospital Museum. O. Œsophagus;  
S. stomach; M. mouth of diverticulum.

neighbourhood of the cardia. Sir Arthur Keith tells us that the wall of the stomach is weak all round its junction with the œsophagus, so that under certain conditions a pouch may develop at some point in this situation as a result of increased intra-gastric pressure. He does not believe that these diverticula are congenital, as other writers have assumed. Our first case seems to confirm his belief, as the patient had had four successive pregnancies artificially terminated on account of the so-called "pernicious vomiting" of pregnancy. It can easily be imagined how a pouch might "blow out" under such conditions at a point where the wall of the stomach is congenitally weak.

Such diverticula are comparable to the much more common diverticula, which occur where a weak spot is present at the junction between the pharynx and the oesophagus. Åkerlund refers in his paper to Keith's statement<sup>5</sup> that diverticula of the stomach occur normally in pigs. But Sir Arthur Keith has shown us specimens of the diverticula of pigs, which differ entirely in their origin from the diverticula which occur in man. They are truly congenital, for Keith has shown that they represent the fundus of the human stomach, which develops as a pouch on the outer side of the cardia, and is eventually separated in pigs by a narrow neck from the rest of the stomach.

True diverticula of the stomach are generally about the size of a cherry. Their walls are formed of mucous membrane, which is generally atrophic, with a very thin and often incomplete layer of muscular tissue, which is entirely wanting in the Guy's specimen, and peritoneum.

Only six cases have hitherto been diagnosed during life with the aid of the x-rays—four by Åkerlund and two by his assistant, Renck. Åkerlund's patients were all women, aged respectively 29, 40, 42 and 58, who were examined on account of symptoms suggestive of gastric ulcer. The diverticulum was always round or oval and in close proximity to the cardia; it varied in size with the amount of opaque meal it contained. In the erect position the food collected in the lower part and showed a horizontal upper limit, above which a gas bubble was visible (Figs. 2 and 3). It was still seen four hours after the meal, when the rest of the stomach was almost or completely empty, but no later examination seems to have been made.\*

The following is the history of our cases.

Case 1.—A married woman, aged 85, complained of attacks of epigastric discomfort, which generally lasted a few days, and rarely occurred except in the winter. The discomfort began about two hours after breakfast; it was relieved by lying down, but not by alkalies. Acid regurgitation, but neither nausea nor vomiting, was occasionally present.

Before coming under our observation she had been x-rayed, and "a definite meniscus was seen at the upper fundic portion," which was still present twenty-four hours later, though the rest of the stomach was empty in five and a half hours. A diagnosis of ulcer was made, and a surgeon advised partial gastrectomy, as he concluded that the ulcer was penetrating the pancreas.

\* Since this was written Dr. E. I. Spriggs tells me that he has seen with the x-rays two uncomplicated cases of diverticula just below the cardiac orifice of the stomach.



FIG. 2.

Diverticulum of stomach (Åkerlund).



FIG. 3.

Diverticulum of stomach—Upper surface of its contents can be seen to be on a level with the lower border of the circular opening into the gas-containing fundus of the stomach (Åkerlund).

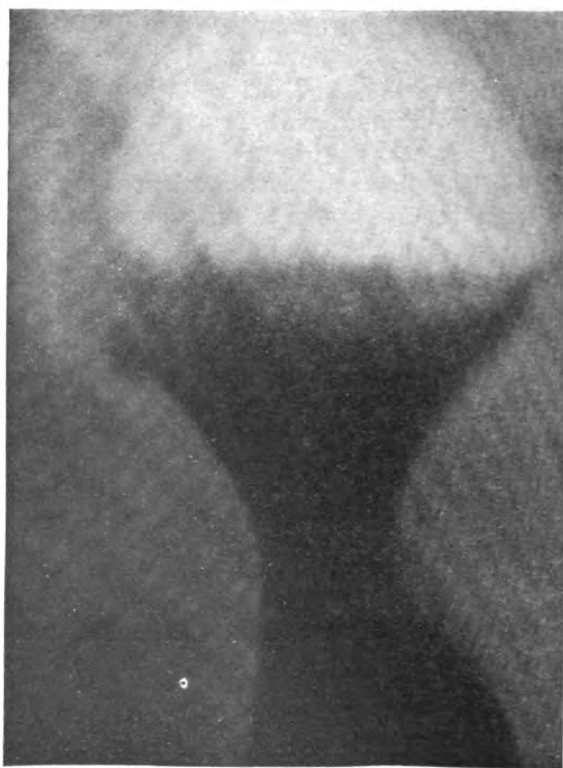


FIG. 4.

Diverticulum of stomach. Radiogram taken immediately after meal.

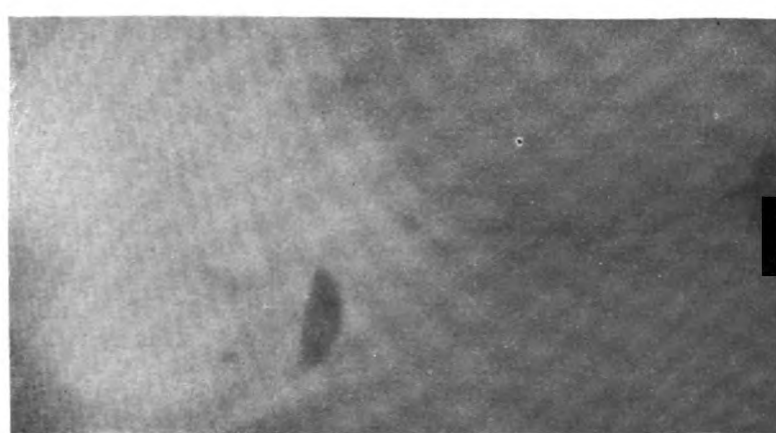


FIG. 5.

Same case as Fig. 4, after six hours: considerable residue still in diverticulum, with very little in most dependent part of otherwise empty stomach.

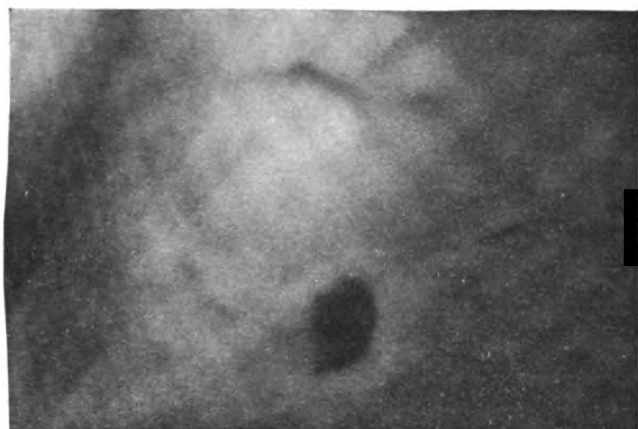


FIG. 6.

Same case as Fig. 5. Diverticulum still full twelve hours after last meal, but not the same meal as Figs. 4 and 5.

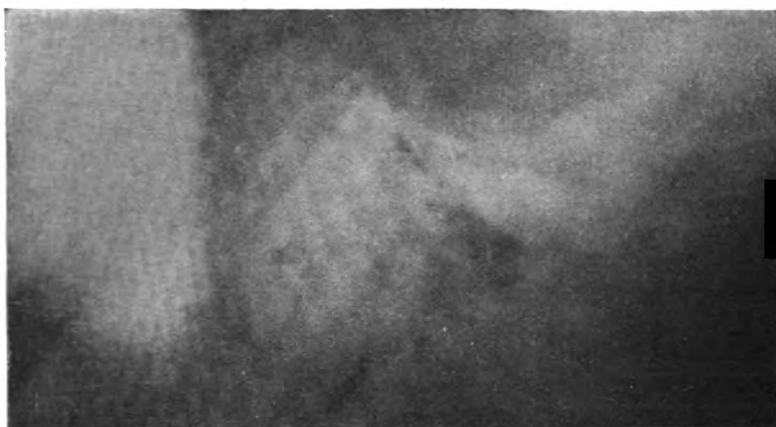


FIG. 7.

Taken five minutes after Fig. 6, after diverticulum had been washed out by manœuvre described in text.

On being referred to us, a diverticulum about the size of a cherry was found in the immediate neighbourhood of the cardia (Fig. 4). It moved freely on deep respiration, and was situated much too high to be connected with the pancreas. On taking a deep inspiration it became accessible to palpation. It was then found to be movable independently of the stomach, to which it was connected by a very short neck. It was globular in shape and not at all tender on pressure. In the erect position the upper surface of the opaque contents was horizontal, and above it was a gas bubble. The opaque contents were still present seventy-two hours after the meal, although the rest of the stomach was empty in less than four hours (Fig. 5).

It seems quite certain that the patient had a diverticulum of the stomach similar to those observed by Åkerlund and Renck. Åkerlund's cases and our case all occurred in women, but only in ours was there a history pointing to how the diverticulum was probably produced. The extreme degree of stasis in our patient's diverticulum would doubtless lead to decomposition of retained food, and it is possible that the morning indigestion was in part due to this. We found that the opaque contents of the diverticulum, seen when fasting in the morning the day after a barium meal had been eaten, could be washed out by drinking a glass of water and then hanging over the side of the couch, with the body inclined first to the right to fill it and then to the left to empty it. By repeating this manoeuvre three or four times in the course of a minute or two the diverticulum was completely emptied (Figs. 6 and 7).

The patient was advised to do this each morning, and also to have her infected teeth treated, as they doubtless were also a factor in producing her indigestion.

Case 2.—A woman, 81 years old, was admitted into New Lodge Clinic for continuous pain under the left costal margin. It was not related to food, and there was no nausea nor vomiting, but she had recently lost her appetite. Three weeks before admission the pain suddenly became very violent; breathing was painful, movement of the left side of the chest was deficient, but no rub was heard, and the temperature rose to between 100° and 102° F. After some hours the pain became less, but it was still present when she was admitted. It was thought at first that localised perforation of a gastric ulcer had occurred, and this seemed to be confirmed by the discovery of an abnormal condition of the stomach with the x-rays. When, however, the examination was repeated at the Clinic, it was found that a diverticulum exactly similar to that discovered in the first case was present immediately below the cardia (Figs. 8, 9 and 10), and that this had been mistaken for the crater of an ulcer.



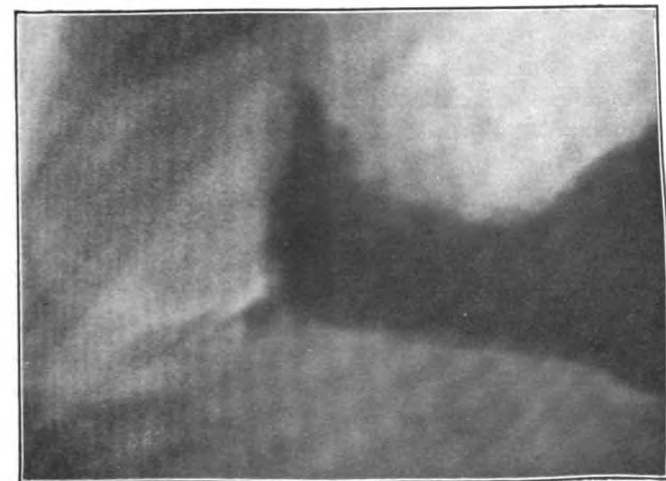


FIG. 8.  
Case of diverticulum of the stomach immediately  
after opaque meal.

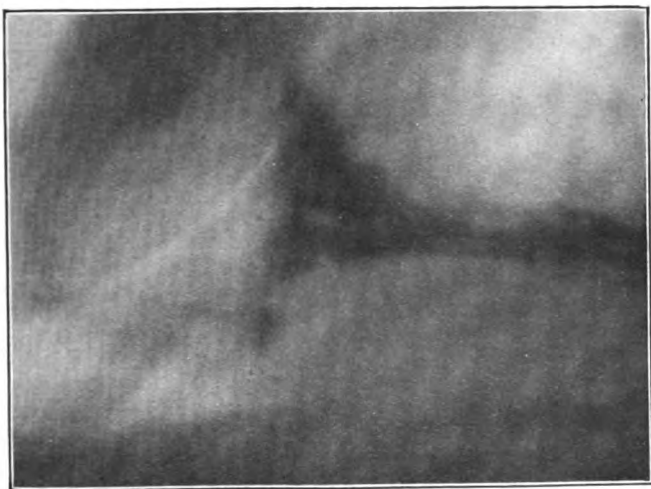


FIG. 9.  
Same case as Fig. 8, taken two hours later.

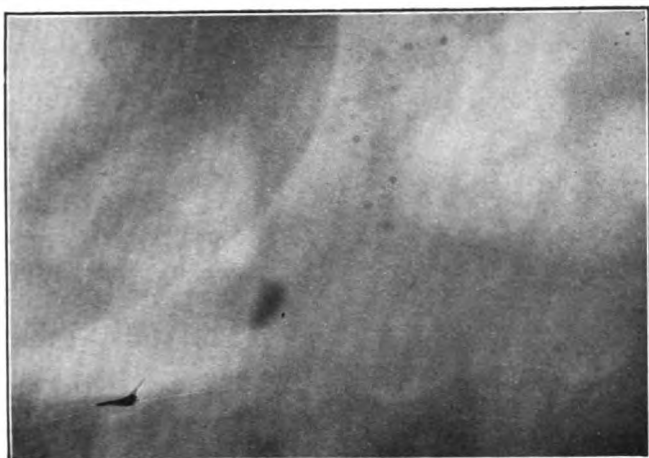


FIG. 10.  
Same case as Fig. 8, taken twenty-four hours  
later.

We concluded that the diverticulum had become inflamed and that perhaps a minute perforation had occurred with the production of localised peritonitis.

A week after her discharge the patient had a sudden copious hæmorrhage, which was thought to be gastric in origin. She was sent to Mr. T. P. Dunhill at St. Bartholomew's Hospital for operation. Further investigation led him to suspect that the hæmorrhage was pulmonary, and the scanty sputum was found to contain tubercle bacilli. A definite abnormal opacity was discovered with the x-rays at the left apex, and on looking at the film taken at the Clinic we found the same appearance, which had unfortunately not been noted when she was with us. There can be little doubt that the attack of pain was due to tuberculous pleurisy, and had nothing to do with the gastric diverticulum.

Fleischner<sup>6</sup> of Vienna has described in the *Klinischer Wochenschrift* for September, 1924,—since the account of these two



FIG. 11.

Radiogram of a diverticulum of stomach, formed of normal mucous membrane and peritoneum, in a man of 62, who died from cerebral hæmorrhage (Fleischner).



FIG. 12.

Radiogram of a diverticulum of stomach, formed of atrophied mucous membrane, atrophied muscle, and peritoneum, in a woman of 75, who died of cancer of the gall-bladder (Fleischner).

cases was written,—the history of two precisely similar diverticula, which he had recognized with the x-rays (Figs. 11 and 12), and in which the diagnosis was confirmed shortly afterwards at autopsy. One of the patients, a man of 62, died of cerebral hæmorrhage; the other, a woman of 75, of cancer of the gall-bladder and liver. In the first case the wall of the diverticulum consisted of mucous membrane and peritoneum only; in the second all the renal coats were present, but in a condition of considerable atrophy.

The remarkable position, even outline, uniform rounded shape, free mobility both with the stomach and to a slight extent independently of it, and the absence of tenderness make the diagnosis of a diverticulum of the stomach easy, when the existence of such a condition is recognised, though in the absence of such recognition a diagnosis of ulcer would appear to be

inevitable in spite of the very unusual features observed with the X-rays.

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## RAREFYING ALVEOLAR OSTEITIS DUE TO *STREPTOCOCCUS PYOGENES LONGUS* (VAR. *VIRIDANS*).

By J. EYRE, M.D., Bacteriologist to Guy's Hospital.

IN connection with cases of oral sepsis, even when probably associated with a rarefying osteitis of the alveolus as indicated by radiograms, there seems to be a fairly general impression that extraction of the teeth implicated will be followed by a cessation of the osteitis and a reparative sclerosis. That this anticipation of events is in many instances based on solid foundation is evidenced by radiograms obtained subsequently. On the other hand, the infective osteitis occasionally progresses, and it is to focus attention on this aspect of the subject that the following cases are instanced.

*Case 1.*—C. T., female, æt. 32, unmarried, suffering from septic polyarthrits and oral sepsis, was admitted into Guy's Hospital for an arthroplastic operation on the right hip. This was performed in January 1923, and at the same time the septic teeth were extracted. The patient was then treated from January to June 1923 with an autogenous vaccine of *Streptococcus pyogenes longus* (var. *viridans*), isolated from the apex of the roots and the root canals of an extracted lower molar with apparently beneficial results. In August 1923 the pain in the affected joints returned with considerable severity, and the patient applied through her doctor for further vaccine treatment. The original antigen was no longer available, as through an unfortunate oversight the cultures had been destroyed. The patient was therefore re-admitted to Evelyn Ward in August 1923 for further investigation. A series of radiograms taken by the dental radiologist demonstrated the continued existence of sepsis, viz. :—

- (1) 7| Small portion of root showing at the gum level.
- (2) |7 Dead tooth, with apical appearances suggesting septic absorption.
- (3) 2.1 1.2 Slight loss of alveolus, with thickening of periodontal membrane.
- (4) Definite and extensive rarefaction of the alveolus in the situation previously occupied by the lower right first and second premolars and the first molar, extracted eight months previously, with a very irregular and "fluffy" outline to the bone, well shown in Fig. 1.

After dealing with the suspicious areas in the maxillæ under a general anæsthetic, my colleague, Mr. A. Bulleid, cut down on the mandibular area indicated in the radiogram and scraped away the soft bone with a Volckmann's spoon down to hard bone. The scrapings were washed with sterile saline solution, and the spicules of bone that were recovered were planted into glucose broth and incubated aerobically at 37° C. for 24 hours. The resulting growth consisted of a pure culture of *Streptococcus viridans*, which subsequently provided the antigen for a new vaccine.

*Case 2.*—Mrs. I. T., æt. 30, first came under observation in 1913 for polyarthritis affecting chiefly the hands, feet and knees of some years' duration, associated with pyorrhœa of  $\frac{7.4}{2}$ . The information was forthcoming that in 1906 the two lower central incisors were extracted on account of obvious pyorrhœa. Local



FIG. 1.

Case C. T. Right lower premolar region.

treatment of the pockets and the use of an autogenous vaccine of the *Streptococcus viridans* for some months was followed by quiescence of the arthritis, and the patient left England. She again came under observation in 1922 on account of further subacute polyarthritis and pyorrhœa most marked in  $\frac{4.1}{5.2} \left| \frac{1.4}{2.5} \right.$ . These teeth were extracted in May and vaccine treatment re-instituted.

As progress was not satisfactory it was decided to extract the remaining teeth, and a start was made in May 1923 upon  $\frac{7.6.5}{7.6}$ . These extractions produced severe constitutional disturbance with exacerbation of all the arthritic symptoms, and it was not until November 26, 1923, that  $\frac{5.6.7}{4.6.7}$  and November 30  $\frac{3.2}{4.3.} \left| \frac{.2.3}{.3} \right.$  were extracted. The arthritis, however, steadily progressed and became associated with fibrositic nodules in the trapezius muscle on each side. In June 1924 radiograms

of the alveolar margins showed a condition similar to that already described, most marked in the lower incisor region and the left premolar region (Figs. 2 and 3), but in this case marked tenderness of the gums was also present, by reason of which the dentures were always giving trouble.

Incisions were made through the gums and the soft bone

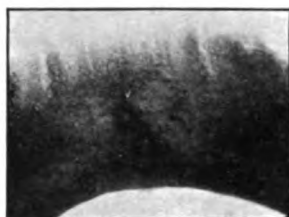


FIG. 2.

Case Mrs. I. T. Lower incisor region.



FIG. 3.

Case Mrs. I. T. Left lower premolar region.

scraped away. Again the spicules after washing in sterile saline when planted into glucose broth yielded a luxuriant growth of *Streptococcus viridans*.

Case 3.—Mrs. P., æt. 41, married, came under observation in October 1921, giving a history of polyarthritis of at least seven years' duration, and on this account had had some twenty



FIG. 4.

Case Mrs. P. Lower incisor region.

extractions in 1914. When first seen at end of 1921 there was pocketing around 3.2.1 | 1.2.3, and cultures from the purulent exudation yielded a growth of *Streptococcus viridans*. These teeth were extracted in November 1922, and from the apex of the root canal of each growth of a similar streptococcus was obtained. Despite treatment the arthritis progressed steadily, and in May 1924 radiograms were taken of both upper and lower jaws. The only abnormality to be detected was in the lower incisor region, where a similar "fluffy" appearance of the edge of the mandible was apparent (Fig. 4).

An incision was made through the gum in this situation and the alveolar margin thoroughly scraped with a sharp spoon. From the soft bone thus removed a pure growth of *Streptococcus viridans* was obtained.

Since the first of these cases many others precisely similar in character have come under observation both in hospital and private practice, but the three described above have been selected in the first place on account of the definite and striking appearances of the prints from the radiographic negatives, and in the second as giving some indication of the length of time after extraction of the associated teeth that the infecting micro-organism can be detected in the diseased bone—8 months, 7 months and 19 months respectively.

For each of the prints, and in two cases for the excellent radiographs from which they were made, I have to thank Mr. C. Worth, of the Guy's Hospital Dental Radiographic Department.

## AN EXPERIMENTAL STUDY OF LEPTOTHRIX BUCCALIS

By ARTHUR BULLEID, L.R.C.P., M.R.C.S., L.D.S. (from the Bacteriological  
and Dental Departments, Guy's Hospital).

It has been noticed for some time that, whenever tartar is found round teeth, *Leptothrix buccalis* filaments are always present. It has been suggested by some observers, notably Goodrich and Moseley,<sup>1</sup> that this organism is essential



FIG. 1.

Direct smear from pyorrhœa pocket. Strands of leptothrix  
jutting out from nodule of soft tartar.  $\times 1000$ .

for the production and deposition of tartar. The verification of the observation itself is simple, since in smears made from material scraped from the tartar ridges around teeth the organism was always found as coarse, generally curved fibres, radiating from a central core of tartar (Fig. 1), in many cases having coccoid bodies scattered between the threads. No smear taken from any situation in which tartar was present failed to show the presence of the coarse leptothrix threads.



The deduction drawn from the original observations, however, appeared to need further investigation. Consequently, a series of observations on the leptothrix was undertaken in an attempt to determine the relationship of the organism to tartar production.

At the outset it was found extremely difficult to obtain the organism in pure culture, and the first isolation was obtained more or less by chance from material scraped from the tartar ridge of an extracted upper wisdom tooth and planted on to ordinary blood agar. Other strains of the leptothrix have



FIG. 2.

Colonies of leptothrix on blood agar plate. Reduced to 7/10ths original size.

since been isolated from various situations, where tartar is commonly found, and grown in pure culture upon saliva blood agar.

#### BIOLOGICAL CHARACTERS

At first the organism could only be grown on saliva blood agar (ordinary 2 per cent. nutrient agar, to which was added sterilised, mixed, filtered saliva, and sterile, citrated rabbit's blood 10 per cent. : reaction 7.4 to 7.6  $P_H$ ). Growth was very slow—in four days it appeared as minute, adherent, discrete, whitish colonies. After repeated sub-culture, alternating plates and tubes, the organism became "media-wise," lost to a great

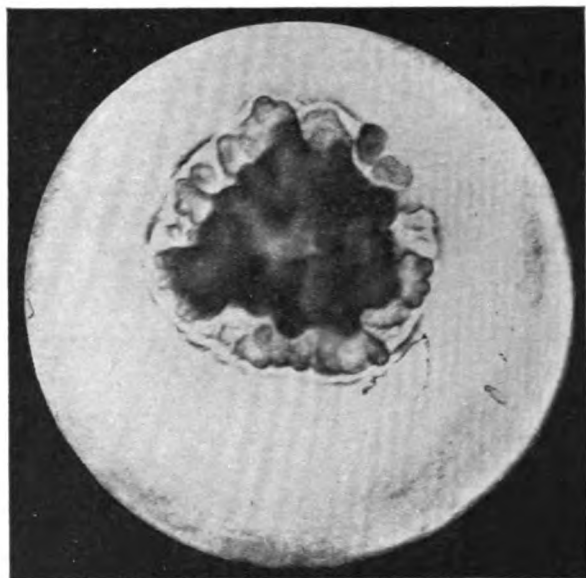


FIG. 3.

Single colony of leptothrix (blood agar plate).  $\times 20$ .



FIG. 4.

Leptothrix strands—showing interlacing of the filaments.  $\times 1100$

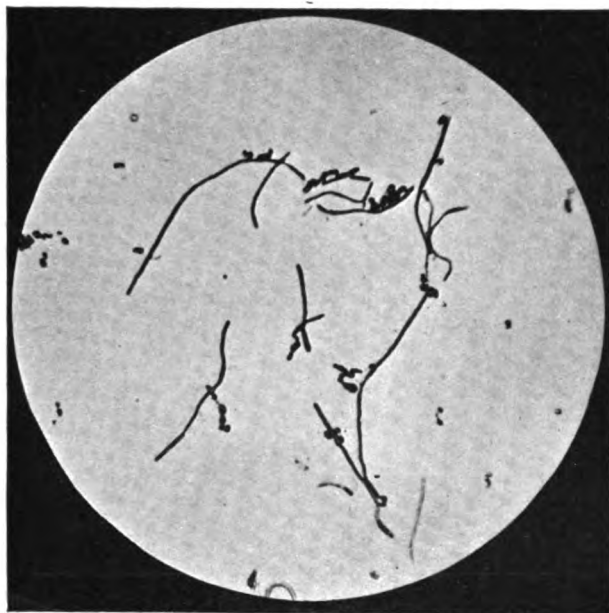


FIG. 5.

Leptothrix strand—with extruded coccoid bodies.  $\times 1100$ .

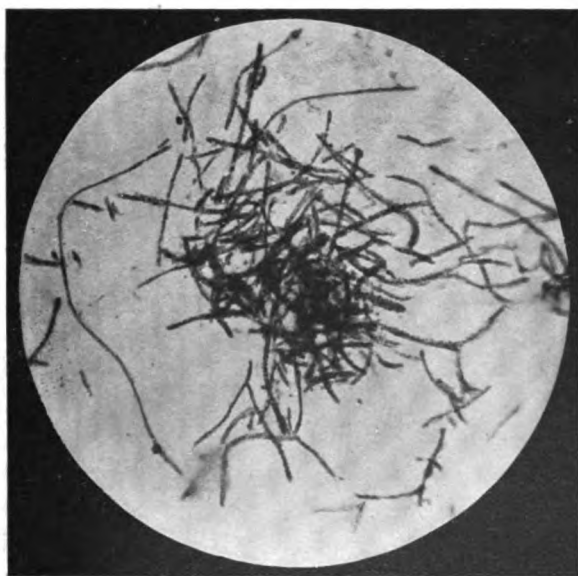


FIG. 6.

Leptothrix—showing granularity of the protoplasm.  $\times 1100$ .  
H H



FIG. 7.

Leptothrix—showing true dichotomy.  $\times 1100$ .

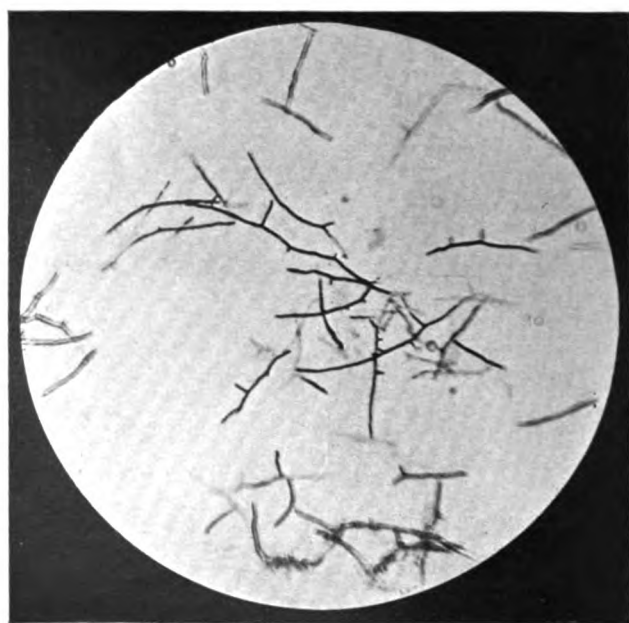


FIG. 8.

Leptothrix—showing false dichotomy.  $\times 1100$ .

extent its adherent properties, and could be cultivated on all the usual laboratory media.

It is a facultative anaerobe, and in primary culture development takes place more rapidly under anaerobic conditions, having an optimum temperature of  $37^{\circ}$  C. It is non-motile and does not form true spores, and it does not liquefy gelatine or form gas.

#### MORPHOLOGY

The organism is pleomorphic, the usual form being that of a long thread showing marked differentiation between cell wall

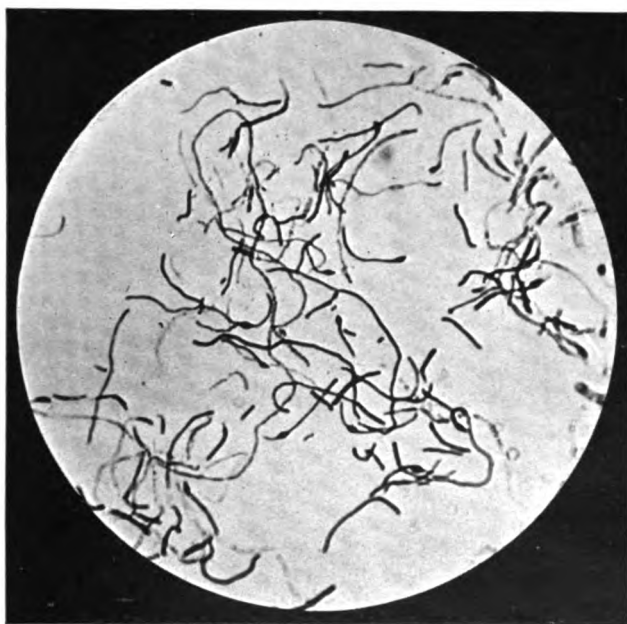


FIG. 9.

*Leptothrix*—showing "clubbing."  $\times 1100$ .

and cell protoplasm. In old cultures this differentiation is accentuated, and the appearance is that of a hollow thread full of coccoid bodies (Fig. 10). The length varies from  $5\ \mu$  to  $60\ \mu$ ; breadth  $0.5\ \mu$  to  $1.5\ \mu$ . It is, as a rule, a curved thread, the various strands crossing each other in a plexiform manner to form a matrix (Fig. 4). Variations of the thread form show true and false dichotomy, branches being generally thinner than the parent stem (Figs. 7 and 8). Sometimes the end of the thread is bacillary and divided into two thinner Y-shaped branches (Fig. 7). Often the thread presents a very granular appearance (Fig. 6).

Other forms met with were—

- (1) threads with clubbed ends (Fig. 9),
- (2) short bacillary forms, generally curved, and
- (3) fusiform rods.

The bottle-brush appearance described by Goodrich was not noted in cultures.

#### STAINING PROPERTIES

The organism is Gram-positive, but strains were isolated in which both Gram-positive and Gram-negative threads were present.

It stains well with all the watery aniline dyes, but shows



FIG. 10.  
Leptothrix—showing hollow thread.  $\times 1200$ .

unequal staining in many cases, particularly with carbolic methylene blue. It is not acid fast.

#### CULTURAL CHARACTERS

(a) *Fluid media*.—*Nutrient broth*: growth is rather poor; forms a slight turbidity which falls to the bottom of the tube as a whitish deposit, leaving the supernatant fluid clear.

*Glucose broth*: growth is similar to that in broth, but is more rapid and more profuse.

*Saliva blood broth*: growth is similar to that in glucose broth, but is even more rapid and more profuse.

(b) *Solid media*.—*Saliva blood agar*: growth appeared as minute, very adherent, greenish-white, pin-point colonies in twenty-four hours; in four days the colonies were the size of a

small pin's head. Very adherent to the medium, raised well above the surface, almost circular in outline, with an inner crenated edge (Fig. 3). In the early sub-cultures the growth was massed and still very adherent to the medium; in later sub-cultures the growth lost the property of adherence to the medium.

*Blood agar*: growth similar to that on saliva blood agar, but colonies took longer to appear (Fig. 2).

*Agar and glycerine agar*: growth only obtained when the organism had acquired the laboratory habit.

*Potato*: almost colourless colonies, rather floury in appearance. Growth scanty.

*Blood serum*: growth was poor; no discoloration and no digestion of the medium.

*Gelatine stab*: growth took place in about four days along the stab and laterally outwards, like a small shrub. No liquefaction of the medium.

## CULTURAL REACTIONS IN SUGAR MEDIA AND LITMUS MILK

	Orig. Lepto.	1	2	3	4	5	6	7	8	9	10	Actino.
Dextrose	±	±	±	0	0	+0	0	0	0	±	0	±
Galactose	±	±	+	±	±	+0	0	0	0	±	+	±
Maltose	±	±	+	0	0	0	0	0	0	0	±	±
Lactose	0	0	+	0	0	distinct alkaline comp. decol.	0	0	0	±	0	0
Saccharose	0	±	0	0	0	slight alkaline	0	0	0	±	0	±
Mannite	0	0	0	0	0	slight alkaline	0	0	0	0	0	0
Glycerine	0	0	0	0	0	alkaline	0	0	0	0	0	0
Dextrine	0	±	0	0	0	decol.	0	0	0	0	0	±
Inulin	0	+	0	0	0	slight alkaline	0	0	0	0	0	+
Litmus Milk	00	00	+0	comp. decol.	++	00	00	00	00	+0	±0	00

## KEY.

*Sugar media.*

0 = No change.  
 ± = Very slight acid.  
 ± = Slight acid.  
 + = Definite acid.  
 +0 = Acid and decolorisation of litmus.

*Litmus milk.*

++ = Acid and clot.  
 +0 = Acid and no clot.  
 ±0 = Slight acid and no clot.  
 00 = No change.

Results were read at the end of one week after aerobic incubation.

The general agreement that existed in the cultural characters of all these strains suggested that they were identical and that one species only had been isolated, and further, that if other species were associated with tartar formation in the human mouth, they had failed to appear in any of the cultures. The next point to determine was whether the artificial cultures of

the leptothrix in fluid media containing calcium salts were associated with precipitation phenomena.

#### CALCIUM PRECIPITATION EXPERIMENTS

(a) *Qualitative*.—2.5 c.c. of 1/1000 sterile  $\text{CaCl}_2$  solution were added to each of several tubes of 10 c.c. nutrient broth. This mixture remained clear, no deposit of phosphates being observed after addition of the  $\text{CaCl}_2$  solution.

This calcium broth was inoculated with cultures of the leptothrix, *Streptococcus brevis*, *Micrococcus catarrhalis* and *Staphylococcus aureus* respectively, and an uninoculated control tube was included in the series. After four days' incubation (anaerobically and aerobically) growth was obtained in all tubes except the control, but only those inoculated with the leptothrix showed any deposit of calcium phosphate.

(b) *Quantitative*.—Quantitative estimations by the Laidlaw-Payne method showed that the actual amount of calcium deposited from the calcium broth in the tubes inoculated with the leptothrix increased with the length of the incubation time.

Three flasks each containing 250 c.c. sterile nutrient broth + 80 c.c. sterile 1/1000  $\text{CaCl}_2$  solution were employed. The first two flasks were inoculated with the culture of leptothrix and all three were incubated at 37° C. aerobically. At the commencement of the experiment all three solutions were clear, but after incubation a deposit was thrown down in the culture flasks. A sample from the first flask was examined at the end of six days' incubation and a similar sample from the second flask after twelve days' incubation. In each instance the sample was centrifugalised at high speed and the deposit then separated from the supernatant clear fluid. The deposit was well washed in distilled water and calcined to destroy the leptothrix and other organic matter. The residue was dissolved in nitric acid and when analysed showed the presence of calcium phosphate.

The calcium content of the supernatant clear fluid was then estimated by the Laidlaw-Payne method. The results were as follows. Each flask contained originally about 8 mg. of calcium per 100 c.c. of fluid. In the six-days sample the calcium content was found to be 1.4 mg. per 100 c.c.—the remainder having been precipitated, presumably as a result of the growth of the leptothrix. In the twelve-days sample the calcium content was 1 mg. per 100 c.c. In the control flask, after twelve days' incubation, the calcium deposit was infinitesimal, whilst the variation in the calcium content of the fluid was within the limits of experimental error.

Further experiments were carried out in order to determine



whether the precipitating action of the leptothrix was due to the action of an extracellular or an intracellular precipitant. A culture of leptothrix 8 on blood agar was subcultured in a tube of broth ( $P_H$  7.6) and allowed to grow for a fortnight aerobically. The culture was then filtered through a porcelain filter and the filtrate tested for possible precipitating action in the following manner. Two rows of six tubes each, together with two controls, were arranged, and into each were put 10 c.c. of nutrient broth + 2.5 c.c. of 1/1000 sterile  $CaCl_2$  solution. The  $P_H$  of the first row was 7.6, and of the second 6.0. Amounts of the filtrate varying from 0.1 c.c. to 1.0 c.c. were added to each of the tubes except the controls and the whole incubated at 37° C. aerobically. After three days' incubation no tube showed any precipitation of the calcium.

Similar experiments were carried out with other strains of leptothrix, but in no case did any precipitation occur.

Next a culture of leptothrix 8 on blood agar was scraped off and mixed with sterile silver sand in a sterile mortar and thoroughly ground up. The mixture was extracted with normal saline and the filtrate collected after passage through a porcelain filter-candle. A similar series of tubes was taken as in the last experiment and the same amounts of filtrate added. After incubation at 37° C. for twenty-four hours a slight precipitate had fallen in all the tubes with  $P_H$  7.6 (except the control), but none macroscopically in the tubes with  $P_H$  6. After a further forty-eight hours' incubation the precipitate had increased in all the tubes with  $P_H$  7.6, and there was also a precipitate in all the tubes with  $P_H$  6, though it was less. This precipitate was found to be calcium phosphate. Both controls remained clear.

A culture of leptothrix 8 on blood agar was scraped off and mixed with sterile distilled water. After incubation at 37° C. aerobically for four days almost complete autolysis had taken place. The filtrate was collected after passage through a porcelain candle. The experiment was conducted in the same way as the two former and almost identical results were obtained.

It is therefore probable that the precipitating action of the leptothrix is due to some property inherent in the actual organism, not in any way to the production of an exotoxin.

#### ANIMAL EXPERIMENTS

In view of these results an attempt was made to stimulate the deposition of tartar on the teeth of healthy cats by the combination of mechanical injury and the implantation of leptothrix cultures. The preliminary technique was the same in all the

experimental animals, and consisted in taking smears and cultures from around the teeth. In the direct smears a few strands of leptothrix were always present, though never numerous. In cultures the only organisms which grew were normal mouth saprophytes.

The cats were invariably anaesthetised with chloroform, and the anaesthesia maintained by the injection of 1 c.c. of a 10 per cent. solution of urethane. The jaws were then propped well open with a cork between the teeth, and next the gum around all the teeth in both jaws was reflected on the external aspect to the depth of a quarter of an inch, as shown in Fig. 11. Reflection of the internal aspect of the gum was found so unsatisfactory that it was not attempted.

In all the cats used (with the exception of the control) cultures of the original leptothrix or other material containing leptothrix were introduced under the gum flap. No sutures



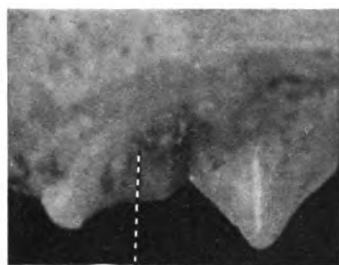
FIG. 11.

were put in, so a certain amount of the culture was no doubt licked away by the cats on coming out of the anaesthetic. The diet was chiefly milk and soft food-stuffs, at any rate for the first few days after the operation.

In all the experimental animals these procedures resulted in the deposition of more or less tartar, and eventually Cat I (control) and Cats II and III (experimental) were killed by chloroform vapour and the jaws dissected out and photographed. It was, however, found difficult to demonstrate the difference between tooth and tartar deposit, and as the teeth in the mandible did not show much tartar, only the upper jaws are reproduced here, enlarged four times (see Figs. 12-17), in which the tartar can be distinguished on careful examination.

*Cat I (Control).*—This animal's mouth was not quite healthy, and there was evidence of a little discoloured tartar on the upper carnassial teeth. As this cat was intended as a control, nothing beyond the incision of the gums was done; it was allowed to come round from the anaesthetic and put back in its

cage. The gums gradually healed up, although for the first few days they looked somewhat sore. After about a five-weeks interval it was noticed that a little extra tartar had been deposited on the upper teeth posterior to the canines, associated with some slight marginal gingivitis (Figs. 12 and 13).

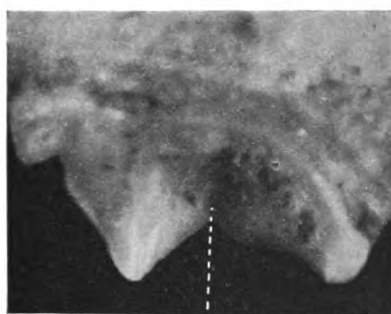


Tags of mucous membrane, and stains on carnassial teeth.

FIG. 12.

Cat No. 1 (control). Right maxilla.  $\times 4$ .

*Cat II (Experiment).*—The teeth were perfectly white and there was no vestige of tartar. The same incision was carried out as with the control cat, but after the gums had been reflected a culture of leptothrix was inoculated under the flap all round



Tags of mucous membrane, and stains on carnassial teeth; also some tartar (very small amount) present before experiment undertaken.

FIG. 13.

Cat No. 1 (control). Left maxilla.  $\times 4$ .

the mouth. About three weeks after the operation tartar appeared round the teeth posterior to the canine (a little round the canines as well) in both upper and lower jaws. Marginal gingivitis was also set up, which increased slightly *pari passu* with the deposition of the tartar. The amount of tartar produced was much more noticeable in the upper than in the lower jaw, but this was probably accounted for by the fact that the

gum reflection was only done on the external aspect of the teeth. Another point noticed was that the tartar produced was brown in colour and that those teeth which did not show much tartar showed marked streaky discoloration.

Soon after the tartar appeared a little was removed with a

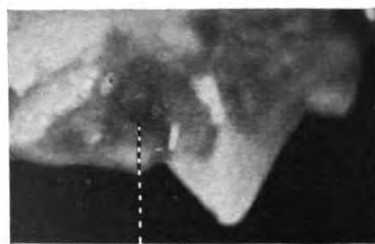


Tartar produced.

FIG. 14.

Cat No. 2. Left maxilla.  $\times 4$ .

scaler and from all appearances seemed to be ordinary hard tartar. On scaling below the gum a softer type of tartar was scraped away and, on staining a smear of this by Gram's method, a large amount of leptothrix was seen.



Tartar produced.

FIG. 15.

Cat No. 2. Right maxilla.  $\times 4$ .

The experiment was repeated about a month after the first experiment—the gum again reflected and a culture of leptothrix put under the flap. Tartar appeared quite quickly in the same situations as before and the marginal gingivitis was now marked (Figs. 14 and 15).

*Cat III (Experiment).*—In this experiment no preliminary incision was made, but a culture of leptothrix in broth was

injected by means of a syringe into the gums around the teeth in both jaws. A very little tartar appeared about three weeks later and the amount of marginal gingivitis produced was very slight.

*Cat IV (Experiment).*—The gums were reflected, as was done with Cats I and II, but instead of the culture of leptothrix,



Tartar produced  
(small amount).

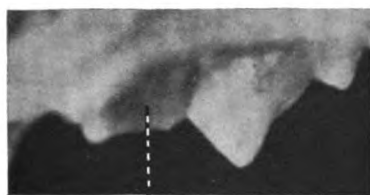
Shows marked staining of canine.  
Little tartar.

FIG. 16.

Cat No. 5. Left maxilla.  $\times 4$ .

a culture obtained from the National Type Collection, consisting of a Gram-negative thread organism (isolated from the eye), was put under the flap. A certain amount of discoloration of the teeth appeared and an almost negligible amount of tartar was produced.

*Cat V (Experiment).*—In this experiment, after incision of



Tartar produced  
(small amount).

FIG. 17.

Cat No. 5. Right maxilla.  $\times 4$ .

the gum margin, instead of a culture of leptothrix being put under the gum flap, some material scraped from a pyorrhœic tooth—which consisted entirely of spirochætes, fusiform bacilli and leptothrix—was introduced. After about a fortnight's interval tartar appeared as before, much more markedly on the upper posterior teeth than on the lower. The discoloration of the teeth and the marginal gingivitis were particularly well marked in this case (Figs. 16, 17).

*Conclusions*

From these experiments there seems some justification for the conclusion that the *Leptothrix buccalis* is an active agent in the production of tartar. Probably for its unrestricted activity certain accessory factors are essential, such as suitable protection, special pabulum, and possibly some particular microbial symbiosis, for it is a fact that in man the existence of a marginal gingivitis is almost invariably associated with rapid and copious deposition of tartar, whilst tartar is absent or insignificant in those whose gums are healthy.

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## DEEP X-RAY THERAPY

By W. L. WATT, *C.M.G.*, M.D.

(From the Deep X-Ray Therapy Research Department, Guy's Hospital.)

THE question as to what constitutes the difference between ordinary x-ray and deep x-ray therapy is so frequently asked that a note of explanation may not be out of place. The truest answer probably is that the former is the slave of the radio-therapist, whilst with deep therapy the radio-therapist is himself the slave. The rays used are so powerful, so often directed towards very susceptible structures in the body, and with so narrow a margin between safety and danger, that the work can never be left even in the hands of a trained lay-assistant for more than a few minutes at a time.

The penetrative power of light rays varies inversely with their length; the longer they are the less, the shorter they are the greater the penetration. Their length progressively shortens as we pass from red to blue, shorter still are the violet and ultra-violet; still beyond these are the soft, the medium, the hard, and the very hard x-rays and the gamma ray of radium.

The degree of hardness of the x-ray depends mainly upon the voltage of the transformer or coil, the degree of vacuum of the tube, and the metallic construction of the anti-cathode or target of the tube itself. From the days of Röntgen, when the rays developed were but slightly shorter than the ultra-violet, uninterrupted improvements have been made. The voltage has been steadily raised, inverse current has been reduced to a minimum, and the discovery of the Coolidge tube revolutionised both tube and coil manufacture, so that apparatuses are now built whose voltage is so enormous that we speak of 200,000 volts in the same way as we did of 20,000 a few years ago.

No tube can stand up to such high voltages unless the current flow is unidirectional, unless it is of extremely high frequency and fine oscillation, and unless it remains steady for long periods of time no matter what variations there may be in the mains from which the primary current is obtained. The apparatus used in this Hospital is capable of producing 250,000 volts and remains steady for uninterrupted periods

of eight hours, although the current used, 200-volt direct, is never constant, the movements of the ampère-needle are never less than one-half an ampère, and for several minutes at a time it frequently swings over an arc of one to one and a half ampères. The solution of these difficulties was found in the discovery of the so-called symmetric apparatus. The principle of this is very simple. Two coils are used, each capable of producing a secondary high-tension current of 100,000 volts or more. One interrupter is used. The positive of the primary current is connected with one coil, the negative with the other coil, so that we have plus 100,000 volts or more on the one side and minus 100,000 volts or more on the other side, a resulting difference of potential between the two sides of 200,000 volts or more.

There are various practical ways of measuring this voltage when the tube is in action, either by a volt-meter, which may or may not be accurate, or by the spark gap. A tube which backs up a spark gap of

30 cm. =	approximately	100,000	volts.
35 cm. =	„	150,000	„
40 cm. =	„	190,000	„
42 cm. =	„	200,000	„
45 cm. =	„	220,000	„

This means that the current will just pass through the tube in preference to jumping the spark gap. An occasional spark indicates that the balance is correct.

The next difficulty to overcome in all types of apparatus from the weakest to the strongest is that the rays emitted are not of uniform hardness. This does not materially matter in the taking of skiagrams, in screen work, and in ordinary skin therapy, but it is of serious import in deep therapy, because the softer rays are absorbed by the skin and subcutaneous tissues, which also have to bear the brunt of the hard rays, so that the effect on the surface is out of all proportion to the amount received at a depth of 10 cm. in the body. The danger of burning or destroying the skin before even an appreciable effect is obtained in the depth is thus very great. To overcome this, filters of various kinds are interposed between the tube and the skin. Those most often used are of zinc and copper, which have practically the same atomic weight. However, as all metals with a higher atomic weight than 27 when exposed to the x-rays themselves emit secondary rays of a hardness corresponding to their atomic weight, it was found necessary to interpose a second filter to



absorb these secondary rays. The filter now used is usually one of aluminium. By the use of these combined filters practically only a homogeneous bundle of hard rays passes through, and it is upon these that deep therapy depends.

We now have to find out what proportion of these rays reach an object at, for example, a depth of 10 cm. from the surface of the body. There are various methods; the simplest is by the ionto-quantimeter. This consists in an electroscope, which is positively charged by friction until the needle moves to a certain marked line on the scale. The electroscope is connected to a long flexible tube, at the free end of which is an ionisation chamber. This chamber is exposed to the rays at a fixed distance of 28 cm. from the target of the tube, negative ions are released which neutralise the positive charge in the electroscope, and the needle returns to zero in so many seconds. A square box, 10 cm. thick, filled with distilled water, the nearest practical equivalent to the tissues of the human body, is now placed between the ionisation chamber and the tube target (new distance 88 cm.), and the time to discharge the electroscope again taken. If the first time was 15 seconds and the second time 60 seconds, then the percentage dose would be  $15/60 = 25$  per cent.; in other words, the remaining 75 per cent. of the rays are absorbed or scattered between the surface and the 10 cm. deep object. The amounts absorbed at 1 cm., 2 cm., and so on have all been carefully worked out, and tables are available for all depths and percentages.

It is now necessary to determine the exact length of time for which it is safe to expose the skin to these highly filtered rays. This can be roughly worked out by using the Sabouraud pastille in the same way as used for the ordinary epilation dose in skin therapy, except that the pastille must be below the filters used. If the time taken to obtain a full B. tint is 25 minutes, we then treat a pelvic case which requires five or more 6 by 8 cm. exposures at a distance of 28 cm.

To field exposure No. 1 is given 28 minutes.

"	"	2	"	24	"
"	"	3	"	25	"
"	"	4	"	26	"
"	"	5	"	27	"

At the end of three days we examine the exposure fields, and whichever one shows a distinct erythema indicates the biological dose for that particular tube under the same conditions of voltage, interrupter frequency, tube mille-ampère, etc. We now can give any case a similar exposure of the same

number of minutes and know that there will be a distinct erythema in three days, and that we have also given 25 per cent. of this amount to a cervix, for instance, at a depth of 10 cm. from the surface.

When larger fields of exposure are necessary, *e.g.*, for the spleen, the tube distance must be increased, and as we know that the intensity of the radiation varies as the square of the distance, tables can be obtained or worked out for all distances, *e.g.* if it takes 25 minutes to give a skin erythema dose at 23 cm., it will take 100 minutes at a distance of 46 cm., because it is twice as far away and the square of two is four.

Allowances have to be made for larger fields of exposure, because owing to deflection and dispersion the deep object receives more rays than if a small field is used. Also the further the tube is removed the more parallel are the rays, the more directly they penetrate the surface of the body, and the less they are absorbed, so more of them reach the deep object.

There are various schools of deep therapy, but the one to which the writer is indebted for all fundamental knowledge is the Erlangen. The underlying principles of this method are as follows, and unless all of them are being carried out, success or failure should not be attributed to the method.

1. A symmetric apparatus with a mercury interrupter, which constantly makes and breaks the primary circuit. 50 times per second.

2. A constant voltage of at least 200,000 volts as measured by a voltmeter or by a spark gap of at least 42 cm. and a constant tube mille-ampère of 2.5 to 3 mille-ampères.

3. Two filters : zinc 0.5 mm. and aluminium 3 mm.

4. A standard tube, which at a distance of 23 cm. through above filters will produce a skin erythema dose in three days in so many minutes and give a 10 cm. depth-dose of a certain percentage. This time and this percentage are periodically tested. All other tubes used are tested by comparison with this standard.

5. A special technique as to position of fields of exposure, their centering and their number, in relation to various parts of the body such as uterus, cervix, breast, etc.

6. The completion of the exposures in each particular case within 24 hours if possible and rarely later than two days.

7. Every change of field of exposure is made by the radio-therapist himself or his confrère-assistant. Under no circumstances are the lay-assistants permitted to do this.

8. Although deep therapy is recognised as a special branch

in itself, its primary function is to assist surgery and in no sense to replace it.

As a result of experience in the treatment and end-results in many cases, this school has given special names to certain percentages of the "skin erythema dose," which for purposes of comparison is given the nominal value of 100. These doses have been found to be the most beneficial for the conditions after which they are named.

Castration dose	=	34	per cent. of the skin erythema dose.
Tuberculosis dose	=	50	" " " " "
Sarcoma dose	=	60-70	" " " " "
Carcinoma dose	=	90-110	" " " " "

The castration dose means that the corpora lutea are destroyed, but not the follicles, so that regeneration is possible in seven or eight years. A 27 per cent. dose to the ovaries causes severe injury to the corpora lutea, which may recover in two years. A 50 per cent. dose to the ovaries causes complete destruction.

The sarcoma and carcinoma doses vary according to the type of cell; the more cellular the growth the more susceptible it is, and the large round or columnar-celled growths are more easily destroyed than the squamous-celled type.

The fact that the intestines, muscles and nerves are very resistant to the rays is of the greatest help in the treatment of deep-seated tumours, because their danger limit is well beyond even the carcinoma dose.

The method of giving a full erythema dose (100 per cent.), for example to the cervix, is by what is known as cross-fire. A full erythema dose is given to the skin, with the rays directed towards the cervix, from five or more areas on the surface of the body. Three from in front, one in the middle line and one from each side, two from behind on the sacral area and one from just below the os pubis. The summation of these will give an erythema dose (100 per cent.) in the depth on the cervix. If each field of exposure has been properly placed and directed, no one area of skin or subcutaneous structures will thus receive an overdose.

# SOME CASES FROM "CLINICAL "

## SERIES II

JANUARY TO MARCH, 1924

*Physicians in Clinical :*

A. F. HURST, M.D., G. H. HUNT, M.D., and C. P. SYMONDS, M.D.

*Clinicals :*

R. B. FAWKES, D.S.O., B.A.	N. W. MACKETH, B.Sc.
S. P. JACOBSON.	B. G. SCHOLEFIELD, B.M.
E. H. KOERNER, B.M.	W. R. SPURRELL, B.Sc.

### A CASE OF CHRONIC INTUSSUSCEPTION ASSOCIATED WITH HYPERPIESIS

By R. B. FAWKES, D.S.O., B.A.

GEORGE M., aged 31, for fifteen years in the printing trade, and employed one week in four in "bronzing"—an occupation which entailed using lead dust—was admitted with a four years' history of regularly recurring attacks of headache, dimness of vision and vomiting, the more recent of which had been accompanied by spasmodic abdominal pain.

During one attack eighteen months before admission he had "seen double" for a period of six to eight hours. He had noticed increasing frequency of micturition both by day and night for the last three years, and said that he had lost two stones in weight since discharge from the Army (category A1) twelve months before the onset of his present trouble.

His earlier history was uneventful.

Points of subsequent interest in the routine examination were his relatively poor physique, the general pigmentation of his skin and the remarkable freedom from oral sepsis.

There was some thickening of the radial and much more so of the retinal vessels, a blood pressure of 220 mm. (systolic) and compensatory left-sided cardiac hypertrophy.

There was fullness in the right hypochondrium—apparently liver—with an ill-defined extension of the "tumour" across the epigastrium.

There was slight bleeding from hæmorrhoids.

Exaggerated knee-jerks with ankle clonus and extensor plantar reflexes were found on both sides, while the abdominal reflexes were inconstant.

During the first twenty-four hours 85 ounces of urine were passed,—acid to litmus, of S.G. 1012, and containing an average quantity of 2.5 parts albumin per 1000, but no blood or casts.

Examination of the blood showed a secondary anæmia with hæmoglobin 70 per cent. and a slight polymorphocytosis. There was no punctate basophilia. The Wassermann reaction was negative. The blood-urea was raised to 0.09 gramme per cent. A similar rise in urea content was the only abnormality found on examination of the cerebro-spinal fluid.

During the period February 24 to March 31, despite dietetic and other general treatment, the blood pressure remained above 200 mm. and the urine much the same in total quantity and albumin percentage as on admission.

On one occasion only were two hyaline casts reported on the daily microscopical examination. The blood urea fell to 0.05 per cent.

Altered blood was on occasions reported in the fæces. Cystoscopy, with intravenous injection of indigo-carmin, showed delayed excretion from the left kidney and ureter, and none from the right.

The "tumour" in the abdomen varied enormously in definition. There was a constant "fullness" in the region of the ascending colon, but the extension across the midline was at times very obvious; at others not demonstrable at all. On one occasion it appeared during palpation and suggested tonically contracting intestine behind obstruction.

The opaque meal showed the "lump" to be extra-gastric, though, with the patient lying on his back, filling of the pyloric end was only possible when the lump was pushed away by palpation.

A barium enema (confirmed on a second occasion when the radiogram here reproduced (Fig. 1) was taken) showed an obstruction, apparently in the lumen of the transverse colon. Along the sides of this a thin layer of the opaque substance could be "milked" by abdominal manipulation. The site of this obstruction coincided with the position of the tumour as felt abdominally at the time.

As it was thought that such definite intestinal obstruction must be aggravating the renal condition, which was now associated with œdema of the ankles and ascites, Mr. Bromley operated on April 4.

A colic intussusception was found with its apex—a point in the wall of the cæcum—lying just short of the hepatic flexure. The ileo-cæcal sphincter with six inches of the ileum and the appendix had been intussuscepted, and the whole could be telescoped round to the splenic flexure. That it had been "riding" to and fro quite easily was demonstrable—the transverse colon being dilated and hypertrophied, while the descending colon was normal.

A single adhesion—in the cæcum and of evidently some months' standing—alone prevented complete reduction. This was divided, the congested appendix removed and the thinned area of cæcal wall which had formed the head of the intussuscepted bowel invaginated. There was no local evidence of

the cause of the original intussusception, but the patient's condition did not allow of the bowel being opened.

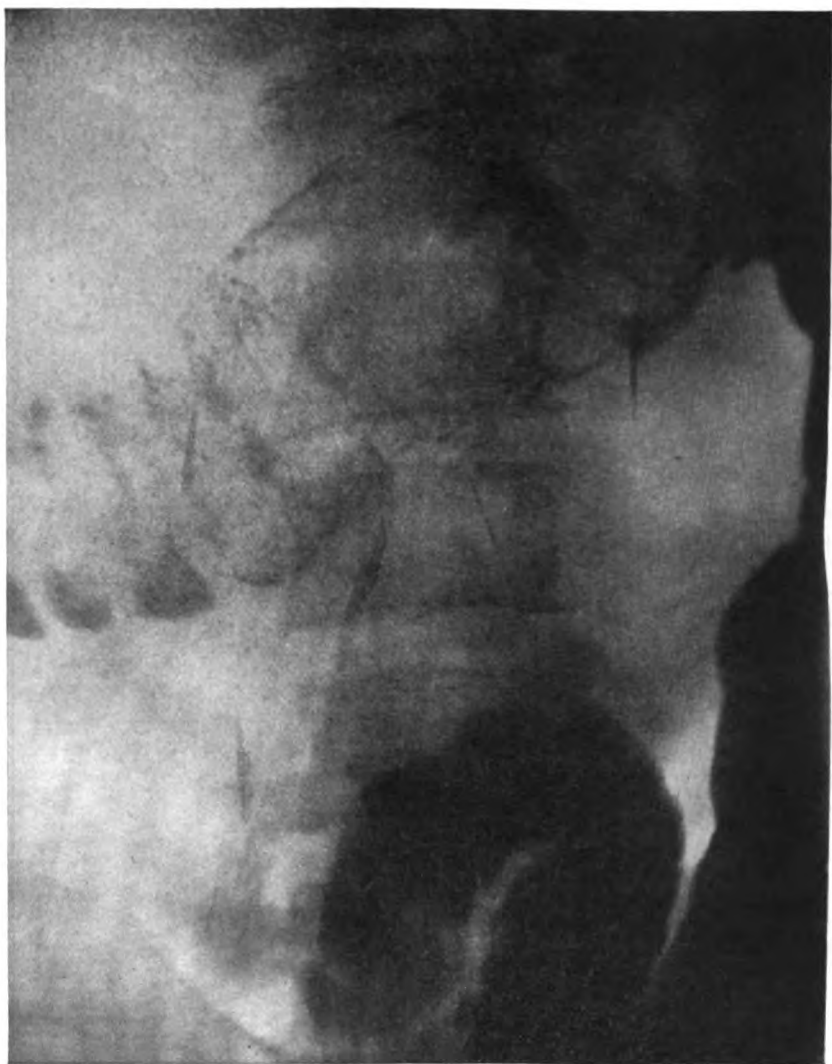


FIG. 1.

Chronic intussusception, visualised after administration of a barium enema  
(Dr. P. J. Briggs).

The liver was ptosed and the kidneys small, with some irregularities on the surface of the left one.

Though the hoped-for improvement in his general condition cannot be recorded, the patient had no recurrence of his abdominal pain and so far recovered from the operation as to be

discharged on May 29. At that time the blood pressure was still over 200 mm., the albuminuria still about 4 to 5 parts per 1000 and the blood urea twice normal. The damage to the kidneys appears to have been irreparable and progressive, for after becoming more and more œdematous, the patient died in uræmic convulsions some two months later.

### *Commentary*

The case, besides illustrating the value of x-rays in the diagnosis of chronic intussusception, suggests another possible factor in the etiology of this relatively uncommon condition. Sir Clifford Allbutt has pointed out that abdominal symptoms are not uncommon in hyperpiesis, and that they, like the attacks of migraine, have their origin in spasmodic contractions of

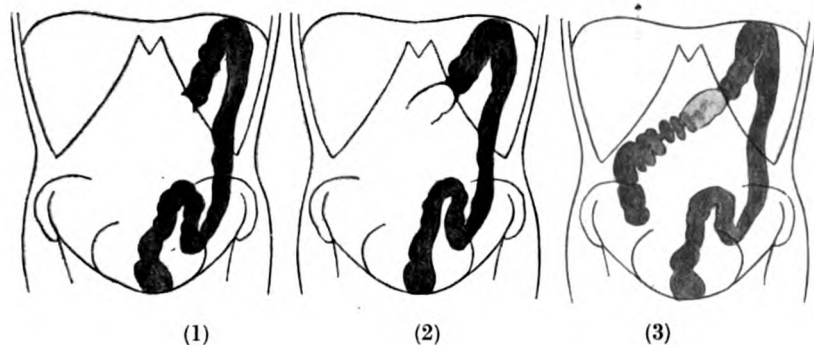


FIG. 2.

Drawings showing stages in passage of opaque enema in case of chronic intussusception. The radiogram (Fig. 1) was taken between stages (2) and (3).

sclerosed vessels—resulting in attacks of pain of anginal character. It is further suggested here that vascular sclerosis and spasm may have initiated the irregular peristalsis which resulted in the intussusception. It was unfortunate that, death occurring away from the hospital, no post-mortem could be carried out to confirm the absence (reported at laparotomy) of any other cause.

Further, as to the specific toxin causing the vascular degenerative process—either primarily or secondarily to its effect on the kidney—repeated negative Wassermann reactions and a negative history eliminated syphilis.

Lead—the next most likely cause from the history—can only be definitely ruled out if the repeated examination for punctate basophilia—the first having been carried out within three weeks of the last exposure to lead—be accepted as sufficient evidence.

For a diagnosis of plumbism, the absence of a “blue line”

could be explained by the absence of oral sepsis, and a case showing pronounced spastic paraplegia definitely due to lead is reported among these cases from Clinical. However, the rarity of such a nerve lesion in lead poisoning, was an argument, if anything, in favour of one of the alternative hypotheses :

- (1) the high blood pressure had caused hæmorrhages, involving both pyramidal tracts, or
- (2) the history of transient diplopia eighteen months previously meant an attack of encephalitis lethargica.

### A CASE OF SPASTIC PARAPLEGIA AND DOUBLE WRIST-DROP DUE TO LEAD POISONING

By S. P. JACOBSON.

THE patient, C. S., 51 years of age, had worked as a solderer for thirty years. His only noteworthy illness was a series of attacks of colicky pains, due, no doubt, to plumbism. In the attacks the pain occurred twice daily and was accompanied by constipation. Lately he had become over-conscientious, living on the premises and working during week-ends. This corresponded in time with the appearance of his symptoms of poisoning.

Difficulty in putting on his right glove was first noticed; then weakness and cramps in his right leg, the left arm and leg becoming similarly affected three weeks later, but not to such a marked extent.

Clinically the case presented the following features. The optic discs and cranial nerves were normal. The upper limbs were weak and wasted. The long extensors of the wrists and fingers were chiefly affected, causing bilateral wrist-drop and drooping of the two middle fingers, the index and little fingers being partially supported by their appropriate extensor muscles. The small muscles of the hands also showed a considerable but less degree of wasting and weakness. The supinator longus on both sides was spared. The muscles of both shoulder girdles were also distinctly wasted and weak, and on admission exhibited fibrillary twitchings. The muscles of the neck and trunk were unaffected. The lower limbs showed no wasting, but all movements were weak, especially those of flexion. Sensation was unaffected. The abdominal reflexes were absent save for an occasional twitch in the left lower quadrant. The knee and ankle jerks were both extremely brisk, the right plantar response was extensor, the left indefinite. Ankle clonus was well marked and sustained on both sides. The sphincter control was unimpaired. The gait was weak and spastic.

There was a typical blue line on the gums with severe pyorrhœa alveolaris.



The patient looked anæmic, and an examination of his blood gave the following results: hæmoglobin 70 per cent., red corpuscles 3,500,000 per cub. mm., and white corpuscles 15,000 per cub. mm., of which the polymorphonucleocytes were 82 per cent. and the lymphocytes 18 per cent. This is not in accordance with the blood picture in most cases of lead poisoning, as lymphocytosis is generally present. But when these investigations were carried out the patient had already left work a month previously. This also presumably explains the paucity of punctate basophilic corpuscles, which, though present, were few and far between.

An investigation of the cerebro-spinal fluid, which gave a negative Wassermann reaction, showed that it contained 0.04 per cent. of protein and 12 cells, all lymphocytes, per c.c. The urea concentration was, if anything, just on the defective side, and the blood urea was 0.07 gramme per cent., but the blood-pressure and size of the heart were normal.

### Commentary

The noteworthy feature of this case is the occurrence of the spastic paraplegia. This condition occurs so rarely that Oliver in his book on lead poisoning does not mention it at all; neither do Luff nor Goadby. In Allbutt's *System of Medicine* Oliver only relates its occurrence in association with the so-called saturnine pseudo-general-paralysis. Morris of Charles-town has described a case in which both the posterior and lateral tracts were degenerated. Amongst eighty-six cases of lead poisoning Putnam formed a group with lateral sclerosis. But none of these were definitely proven to be due to plumbism, and the author himself held that he had formed no clear case. Similar cases were described by Bechtold and Oppenheim. Kinneir Wilson has described four cases closely resembling amyotrophic lateral sclerosis. Three of these were, in fact, diagnosed as such. But he too, to me, does not seem to have proven with certainty that lead was the causal factor. In only one case was a blue line noticed, and it was not a definite one, and the presence of punctate basophilia is not mentioned.

The blue line, punctate basophilia, and anæmia which occurred in the above case are unequivocal signs of plumbism. The lymphocytosis occurring in the cerebro-spinal fluid does not seem to have been reported before. It is worth noting that the Wassermann reaction of the cerebro-spinal fluid was negative, as various authors have described cases of plumbism of the central nervous system that gave positive reactions in the cerebro-spinal fluid, although syphilis was definitely excluded.

An examination of the patient after four months of electrical

treatment, the administration of potassium iodide and the wearing of splints for his dropped wrists showed that the paralysis had greatly improved, and the gait too was not so abnormal. The reflexes, tremor and blue line remained as before.

## A CASE OF LYMPHOCYTIC LEUKÆMIA, WHICH WAS AT FIRST ALEUKÆMIC

By E. H. KOERNER, B.M.

ALFRED J., aged 80, was admitted into Addison Ward on February 5, 1924. He gave a history of nine weeks' progressive exhaustion and anæmia, and his doctor sent him up with the provisional diagnosis of Addisonian anæmia.

On admission he was extremely pale, and his complexion had a faint yellow tinge. The skin of his abdomen showed slightly raised pigmented areas about the size of a sixpenny-piece, of a pale slaty-grey colour. These pigmented areas faded in a fortnight.

Examination of his heart showed a systolic murmur in the pulmonary area, and a reduplicated second sound at the apex. The spleen was just palpable; there was no evidence of any enlarged lymph glands. Blood examination showed a hæmoglobin percentage of 18, a red cell count of 1,072,000 per cub. mm. with some anisocytosis, but no normoblasts or megaloblasts. There were 2,300 white cells per cub. mm., of which only 16 per cent. were polymorphonuclears, 68 per cent. being lymphocytes (large and small), 9 per cent. transitional cells, 11 per cent. lymphoblasts, and 1 per cent. hyalines. No eosinophil or basophil cells were seen. Van den Bergh's test gave a faintly positive indirect reaction. The Wassermann reaction was negative. There was no trace of gastro-intestinal hæmorrhage revealed by examination of the stools, neither were ova detected, which might have accounted for the patient's anæmia. Fractional test-meal showed slight hyperchlorhydria. The urine showed no abnormality. There were no retinal hæmorrhages.

On the third day after admission the patient was transfused with 500 c.c. of blood taken from his brother, whose blood belonged to same group; twenty-four hours later, there was a sharp rise of temperature to  $103^{\circ}8$ , and the patient showed signs of sepsis of his mouth and throat. This infection subsided after three days, and the condition remained stationary until early March, when there occurred another rise of temperature followed by ulceration of the tongue and lower lip, from which *Staphylococcus aureus* and *Streptococcus longus* and *brevis* were cultivated.

On both these occasions of febrile reaction blood cultures proved negative. At this stage the patient's condition grew very alarming; he was given an immuno-transfusion of 500 c.c.

of defibrinated blood,\* and an injection of 0.45 gramme of N.A.B. Three days later the ulcer had healed, and the temperature was normal. After a fortnight's salvarsan treatment the hæmoglobin had risen to 32 per cent., the total red cell count being 1,800,000 per cub. mm., and the white cell count 8,800 per cub. mm., of which 40 per cent. were polymorphonuclears. Altogether, the patient had 1.5 grammes of N.A.B.; he progressed satisfactorily and was discharged in May with a hæmoglobin percentage of 80, and a red cell count of 5,360,000 per cub. mm.

The patient was re-admitted on July 15. The spleen was definitely palpable, and there were several enlarged lymph glands in the neck and axillæ. His abdomen and back showed numerous pigmented nodules; a section of one of these showed an infiltration of the subcutaneous tissue with lymphocytes, especially around the vessels, suggestive of leukæmia. The hæmoglobin had fallen to 37 per cent., and the red count to 1,112,000 per cub. mm.; the total white cell count had now risen to 87,500 per cub. mm., of which there were:

Polymorphs	.	.	.	5.5 per cent.
Lymphocytes	.	.	.	17 „
Hyalines	.	.	.	0.7 „
Lymphoblasts	.	.	.	72.6 „
Myeloblasts	.	.	.	4 „
Eosinophils.	.	.	.	0.2 „

The oxidase reaction showed that the abnormal forms were almost entirely lymphocytic in type.

Further salvarsan treatment produced no improvement; at the end of July the hæmoglobin percentage had fallen to 14; the patient was unable to take food and he died on the 31st.

The post-mortem examination showed infiltration of the lymph glands along the aorta and bronchi; the heart showed "tabby cat" striation; the liver gave the Prussian blue reaction; lymphoid deposits were found in the kidneys; microscopical examination both of these and of the lymph glands showed the characteristic appearance of lymphatic leukæmia.

### *Commentary*

The diagnosis of this case in its early stages presented considerable difficulty. Causes of anæmia such as internal hæmorrhage, poisons and parasites being eliminated, the diagnosis had to be made from infective endocarditis, Addison's anæmia, or a hæmolytic anæmia of toxic origin. The unvarying character of the heart murmur, together with the absence of emboli and the repeatedly negative blood cultures, did not

\* The donor, a man of the same blood-group, was given a subcutaneous injection of 500 million staphylococci; four hours later 500 c.c. of his blood were defibrinated and transfused into the patient.

warrant the diagnosis of infective endocarditis. The fact that there were no gastric or nervous symptoms and signs, and the absence of large red blood corpuscles, as shown by Price-Jones' curves (only one red cell measuring  $9\ \mu$  was found), together with a definite hyperchlorhydria and an only faintly positive indirect Van den Bergh reaction made Addison's anæmia very improbable.

As regards the white cell count in the early stages, a low leucocyte count with a relative lymphocytosis and absolute reduction in the number of polymorphonuclears might be consistent with Addison's anæmia. Relative lymphocytosis, together with the presence of lymphoblasts and pigmented areas in the skin, were the only signs which might at first have suggested an aleukæmic leukæmia.

It would appear as if the toxic process causing hæmolysis over a prolonged period had ultimately caused exhaustion of the bone marrow, giving the clinical picture of an aplastic anæmia. Blood transfusion and salvarsan treatment seem to have tided over the most dangerous period of the illness, and to have raised the hæmoglobin sufficiently high for the bone marrow to take up the task of producing new red cells. It is interesting to consider whether the same process may have caused hæmolysis, aplastic anæmia, and over-action of the lymphoid tissue.

The case, though it began as one of "aleukæmic leukæmia," was not so throughout, because a typical leukæmic blood picture was present when the patient was readmitted, with enlarged lymph glands and a definitely palpable spleen.

J. M. H. Campbell and J. J. Conybeare in the *Guy's Hospital Reports* of 1922 described as "leukanæmia" the case of W. V., aged 27, admitted in 1910 under Dr. Beddard. "Five years before, the glands in his neck had enlarged, and gradually glands in groin and axillæ also enlarged. Spleen could be felt 2 inches below costal margin; hæmoglobin was 26 per cent., C.I. 1.4; white cells numbered 16,000, of which 80 per cent. were lymphocytes. Before his death, white cells had risen to 177,000, of which 90 per cent. were lymphocytes. Post-mortem, there was found general enlargement of lymphatic glands, including mediastinal and mesenteric glands. Bone marrow was red, and liver and spleen gave a marked Prussian blue reaction."

Here, enlargement of lymph glands seems to have been the earliest sign, and there presumably was a blood picture of Addison's anæmia; neither of these points was observed in the case of Alfred J.

The development of ulcers on the tongue, palate and lips due to sepsis favoured by the scarcity of polymorphonuclear cells is of relatively frequent occurrence in leukæmia; in a number of cases, Vincent's spirillum and fusiform bacillus were grown; these organisms were absent in this particular case.

As regards treatment, the first blood transfusion appears to have had but little effect. On the second occasion, the patient was given an immuno-transfusion of defibrinated blood taken from the same person, and this was followed by an injection of N.A.B.; rapid improvement followed. The bactericidal power of the blood was examined by Professor Adrian Stokes before and after the second transfusion, but there was no marked change. Throughout the disease, administration of arsenic by mouth proved of no value.

## A CASE OF ALEUKÆMIC LYMPHOCYTIC LEUKÆMIA

By W. R. SPURRELL, B.Sc.

FRANK H., 42, a clerk, was admitted on January 28, 1924, for swellings in the neck, axillæ and groins, accompanied by a feeling of lassitude and general malaise.

He had been quite healthy up till the war: he contracted dysentery in 1915, but recovered completely in six weeks, and was wounded in 1916 and 1917 with loss of his right eye. In 1920 he contracted syphilis, but received immediate treatment with salvarsan, and had since had four negative Wassermann reactions.

On December 23, 1923, he had a "feverish attack," but no coryza or sore-throat. During the following week the glands in his neck, axillæ and groins began to enlarge and he felt vaguely unwell and disinclined to work. There was some looseness of the bowels, but no dizziness or dyspnœa. This condition persisted up to the time of admission.

On examination chains of glands could be felt along both sterno-mastoid muscles, and in both axillæ and groins; the glands were discrete, freely movable, elastic and neither tender nor hot. The abdomen was very prominent, but no free fluid could be detected. A feeling of fullness in the right iliac fossa suggested the presence of a tumour. The spleen was enlarged, its lower pole being two inches below the costal margin; the liver edge was palpable. The chest moved well and evenly; the breath sounds at both bases were very harsh. There was no pyrexia, and the urine was normal.

Hodgkin's disease, lymphatic leukæmia, tuberculosis or glandular fever were the suggested diagnoses.

On January 29 the red cells numbered 3,560,000 per cub. mm., with 88 per cent. hæmoglobin, giving a colour-index of 1.2.

The white cells numbered 2,700 per cub. mm.; 45 per cent. were lymphocytes.

On February 4, Mr. L. Bromley removed one of the cervical glands; it was adherent to the surrounding structures, suggesting an infiltrating growth. On section the gland was reported to be lympho-sarcomatous and to infiltrate the surrounding tissues.

The cervical glands grew smaller, but the abdomen became more distended. There was much gastro-intestinal discomfort with retching and diarrhœa, and dyspnœa developed. The spleen became larger, and a rub could be heard over it.

On February 6 the blood picture showed red cells 3,670,000 per cub. mm. with hæmoglobin 88 per cent., giving a colour-index of 1.18; several megaloblasts were seen. The white cells numbered only 2,100 per cub. mm.

A test-meal gave a normal curve for free acid. Van den Bergh's test gave a positive indirect action.

Edema of the legs, scrotum and lumbar region developed, and free fluid could be detected in the abdomen; the dyspnœa became severe, but the patient still declared he felt well.

On February 12, Messrs. Hampson and Shackle examined the patient's blood and reported as follows:

Red cells 4,670,000 per cub. mm.; hæmoglobin percentage 92; colour-index 0.97.

White cells 4,700 per cub. mm.:

Polymorphs	.	.	.	24 per cent.
Lymphocytes	.	.	.	57 "
Hyaline cells	.	.	.	10 "
Myelocytes	.	.	.	9 "

Nucleated red corpuscles, chiefly megaloblasts, were present up to 8 per cent. of the white cells. Polychromasia, punctate basophilia, poikilocytosis and some anisocytosis were present, the blood being distinctly megalocytic in type.

On February 17 the patient's temperature suddenly rose to 102°, dyspnœa became still more marked, and progressive heart-failure with cyanosis led to death in eighteen hours, apparently owing to an acute terminal infection, which coincided with an acute infection in two adjacent beds.

At the post-mortem general soft, hæmorrhagic enlargement of lymph glands was found. The thymus formed a large tumour, and there was another mass behind the stomach. The spleen was very much enlarged and contained many infarcts; the liver was enlarged and pale, and gave the iron reaction. The duodenum and jejunum were infiltrated with lymphomatous nodules. The bone marrow was red. Sections of these tissues showed marked lymphocytic infiltration, similar to that of lymphatic leukæmia. In view of the persistent low white count, and the generalised leukæmic findings at the post-mortem, the case was considered to be one of aleukæmic lymphocytic leukæmia.

*Commentary*

The short history and the enormous lymphatic deposits found post-mortem point to a very acute process—the aleukæmic condition of the blood might conceivably be a “negative phase” in the development of the blood picture usually seen in leukæmia, which in this case was prevented by the rapidly fatal progress of the disease. This view receives support from the slowly rising white count with its relative and absolute rise in lymphocytes. In the scanty literature on this subject cases are recorded in which a preliminary leucopenia has developed into a typical leukæmia and vice versa, but the pathology of the process is completely obscure.

The rising red cell count with its distinctly megalocytic characteristics, together with the indirect Van den Bergh reaction, the positive iron reaction in the liver and the red marrow, suggest a reaction to some severe hæmolytic process. Some of the cases classed as “leukanæmias” have presented blood pictures of a similar type.

#### A CASE OF MYELOCYTIC LEUKÆMIA TREATED BY DEEP X-RAYS

By B. G. SCHOLEFIELD, B.Sc.

THOS. G., aged 53, was admitted to Addison Ward in February 1924. He had always been healthy until in August 1923 he began experiencing some difficulty in taking a deep breath. He was seen by his private doctor, who made a note that the spleen was enlarged. Later in the year a further note on his medicine sheet stated that the spleen was growing. When admitted in February it was enormous, reaching forwards half an inch to the right of the mid-line, which its lower border crossed four inches below the umbilicus. The anterior edge, which was sharp and had two notches, could be seen moving up and down with respiration.

Except for the inconvenience caused by this large mass in the abdomen, which made stooping difficult and somewhat hindered his breathing, the patient felt and looked perfectly fit. He had acne rosacea, but otherwise was of a good colour. The respiratory, cardiovascular and central nervous systems showed no abnormality. The liver was enlarged, the lower edge being palpable one inch below the costal margin.

His hæmoglobin at this time was 55 per cent. and the red cell count 4 million per cub. mm. The white cells numbered 240,000 per cub. mm. and were of very abnormal type. There were a few lymphocytes, perhaps as many as in normal blood, and about the same number of eosinophils, so that these latter

cells were definitely in excess. The bulk of the leucocytes were myelocytic in type, and every gradation from true polymorpho-nuclear cells to myelocytes were to be found. An accurate differentiation was impossible, but, dividing them into groups, there were present :

Polymorphs	.	.	.	84	per cent.
Transitionals	.	.	.	12	„
Myelocytes	.	.	.	47	„
Basophils	.	.	.	5	„
Lymphocytes	.	.	.	} 2	„
Eosinophils.	.	.	.		

In spite of this very abnormal blood picture, the patient felt perfectly fit, and there had been no tendency to hæmorrhage either externally or into the gut.

On February 27, Dr. Watt treated the patient by means of deep x-rays, the area of skin over the spleen being exposed for 35 minutes. The patient experienced no discomfort afterwards, and two days later was convinced that the swelling was smaller in his abdomen. On examination the spleen still extended as far forward as before, but the anterior edge had become softened and rounded and was difficult to feel. The number of white cells in the blood had, however, decreased to 64,000 per cub. mm., *i. e.* a quarter of their original number, and a differential count showed 60 per cent. of true polymorphs, with only 80 per cent. of cells of abnormal types.

By March 2, four days after exposure, the spleen had definitely shrunk, falling short of the mid-line by fully an inch. On March 4 the patient was discharged, with a white cell count of only 25,000 per cub. mm.

This man has since been under the care of Dr. Watt and Mr. Carter Braine, who have kept a close watch on the blood picture. After leaving the hospital the leucocytosis gradually disappeared, and the cells assumed a normal type. The spleen has never become impalpable, but is now confined to the left hypochondrium. In June his white count again started to rise, and he was given a second exposure to the x-rays. A fuller account of this case amongst others is being published in the *Lancet* by Dr. Watt, and it is through his courtesy that I am able to write a short account here.

#### A CASE OF MYELOCYTIC LEUKÆMIA TREATED BY SPLENECTOMY

By S. P. JACOBSON.

THE patient, K. S., aged 24, was admitted into Guy's Hospital in March 1923, complaining of a tumour in her abdomen and of six months' amenorrhea. There were no subjective symptoms except the discomfort caused by the tumour.



An examination revealed a hard lump extending between the left costal margin and the brim of the pelvis. On vaginal examination the tumour was felt distinct from the uterus in the pouch of Douglas.

A laparotomy was performed, and the tumour was found to be an enlarged spleen normal in colour and consistency. It was easily delivered and removed, as it had formed no adhesions. The patient made a good recovery and went back to her work. Her periods returned in July and have been normal and regular since.

On section the spleen showed œdema and myelocytic infiltration.

A series of blood examinations, commenced immediately after the operation, gave the following results :

	Red cells. per cub. mm.	White cells. per cub. mm.
March 14	3,200,000	200,000
March 17	3,300,000	100,000
March 21	2,200,000	146,000
March 28	3,600,000	131,600
April 7	3,100,000	74,000
June 6	2,900,000	47,000
Sept. 4	2,416,000	121,600

A differential count of the white cells showed 41 per cent. to be polymorphonucleocytes and 50 per cent. to be myelocytes. All gave a strongly positive oxidase reaction. Many nucleated red cells were present.

About a year after the spleen was removed the patient still considered herself perfectly well and continued at her work as usual, but it was thought wise to subject her to x-ray treatment over her long bones. After four months her white and red cell counts were within normal limits.

#### *Commentary.*

The first two splenectomies for leukæmia were performed by Thomas Bryant<sup>1</sup> in Guy's Hospital in 1866 and 1868. Both cases are fully described in the "Reports." The first case died two hours after the operation from a ruptured vein, and the second case fifteen minutes after from hæmorrhage due to ruptured adhesions. From these cases Bryant drew two conclusions. First, that the operation was too precarious from the point of view of hæmorrhage, and second, that even if the spleen was removed the disease was not cured, as the same pathological changes seemed to be present in the lymphatic glands. In Bryant's cases the blood under the microscope seemed to consist of as many white as red cells, but whether they were lymphocytes or myelocytes we do not know. Thus one

or both of the cases may have fallen under the category of lymphatic and not myelocytic leukæmia. They were, however, definitely not cases of splenic anæmia, and as the spleens were very large, they were most probably of the myelocytic variety.

Up to the year 1900 the mortality in cases of splenectomy for leukæmia is said to have been 90 per cent. In 1918 Griffin<sup>2</sup> collected fifty-one cases, of which forty-three died at once or very shortly afterwards. Of the eight survivals, four were soon dead. The cause of death in nearly all cases was hæmorrhage. In some cases the abdominal wound did not heal properly and ventral hernia resulted. It is not to be wondered at that surgeons all over the world protested against such surgery.

It was not many years, however, before the operation was again performed, and with better technique the mortality dwindled greatly.

Griffin reported the result obtained in twenty-six cases at the Mayo Clinic. In the majority the spleen was previously exposed to radium in order to reduce its size and reduce the number of white corpuscles. Only one patient died as a direct result of the operation. Five remained in good health and two in fair health from three to five years after splenectomy, and thus outlived the life expectancy of the disease. Griffin regards the operation as justifiable for the comfort of the patient in very chronic cases, in which preliminary radiotherapy has had a favourable effect on the size of the spleen and on the blood picture, but there is no evidence that the duration of the disease is definitely lengthened by splenectomy.

#### REFERENCES

- <sup>1</sup> T. Bryant: *Guy's Hosp. Rep.*, 3rd series, xii. 444, 1866; and xiii. 411, 1868.
- <sup>2</sup> H. Z. Griffin: *Med. Record*, xciv. 1020, 1918; and *Reports of Mayo Clinic*, 1922.

### A CASE OF CARCINOMA OF THE STOMACH, PROBABLY SECONDARY TO A GUMMA

By E. H. KOERNER, B.M.

MRS. EMMA S., aged 45, was admitted to Mary Ward in February 1923, giving an eighteen months' history of pain in the epigastrium, occurring one or two hours after meals and lasting about twenty minutes. This pain, which was of a dull aching variety, was also felt in the back under the shoulder-blades. These attacks were often followed by eructation, which gave some relief. The patient had had hæmatemesis on two occasions, and stated she had lost three or four stones in weight, and that, five months before admission, she had noticed some lumps on the left side of her chest.

Abdominal examination showed a large lump in the epigastrium, moving freely on respiration. Its lower edge could

be felt from one to two inches below the left costal cartilages; its outline was slightly curved, the convexity being directed downwards, and there was some tenderness on pressure.

Enlarged glands could be felt in the left axilla and deep to the sterno-clavicular end of the left sterno-mastoid. Three distinct lumps could be felt on the left side of chest in the mid-axillary line at the level of seventh rib; each of these was about the size of a walnut; the skin could not be raised off their surface, but they were not attached to underlying ribs. They were moderately hard, well circumscribed and not painful or tender. The breasts were normal, and rectal examination showed no abnormalities.

A fractional test-meal showed pus and red cells in the resting juice; the total acidity and free hydrochloric acid curves were within the usual limits. Chemical examination of the faeces showed the presence of a considerable amount of altered blood. An x-ray examination showed an orthotonic stomach exhibiting vigorous peristalsis; there was some irregularity in its outline towards the cardiac end, and some tenderness on pressure along the lesser curvature about two inches from pylorus, with a slight irregularity at this point. The barium meal passed readily through the pylorus.

As the patient gave a history of several miscarriages, a Wassermann test was performed and gave a strongly positive reaction. The case was diagnosed as carcinoma ventriculi with secondary deposits in the axilla and above the clavicle; the lumps in the left axillary line were supposed to be outlying lymphatic glands with secondary deposits. The patient was discharged as inoperable after ten days, but owing to her Wassermann reaction being strongly positive, her doctor was advised to administer massive doses of potassium iodide.

The patient was re-admitted in February 1924: her epigastric pain was now so sharp at times as to oblige her to lie down; it would come on at irregular intervals, and was no longer related to meals. A fortnight before re-admission she had brought up about one ounce of bright red blood. She had lost her appetite, but, provided she ate slowly, she had no trouble in retaining food of a semi-fluid variety. She had lost two stones during the last twelve months.

Abdominal palpation showed a tumour similar to that found a year previously, but there was now also a rounded lump on the right side of the mid-line just above the level of umbilicus; this did not move on respiration and seemed to be independent of the stomach; it was suggestive of a mass in the omentum. The three lumps over the left chest had entirely disappeared, but the glands in the left axilla and above the left clavicle were still present. Examination of the liver and rectum showed nothing abnormal.

Several unsuccessful attempts were made to pass a stomach tube, the bulb on every occasion not going beyond the cardia. This was found by the x-rays to be due to obstruction at the cardiac end of the stomach (Fig. 3). There was a second

obstruction in the mid-gastric region; peristalsis was only present in the lower portion; there also appeared to be an obstruction in the third part of duodenum. The stomach, however, emptied in four hours.



FIG. 3.

Case of cancer and syphilis of the stomach (Dr. P. J. Briggs).

Examination of the stools again showed the presence of a considerable quantity of altered blood, and the Wassermann reaction was still strongly positive. A supraclavicular lymph-gland was removed, and microscopic examination showed

changes typical of a carcinomatous gland. However, a further course of potassium iodide and salvarsan was given; this was followed by slight improvement, and the lump in the right epigastrium seemed to become less obvious. The patient was again discharged as being inoperable.

The patient's doctor has since reported her further history as follows: "She kept in bed after coming home. She steadily emaciated, and the abdominal lumps became more plainly felt and painful, with frequent sickness. She died at the beginning of August."

The somewhat unusual history and x-ray appearances of this case, together with the improvement following specific treatment, might suggest that it was a case of carcinoma following a gumma of the stomach, and illustrate the importance of performing a Wassermann reaction in all cases of suggested carcinoma ventriculi.

A gumma may clinically simulate a carcinoma, and a syphilitic ulcer may simulate a duodenal ulcer. The resemblances to carcinoma include the presence of a palpable tumour in the epigastrium; the occurrence of loss of weight and cachexia, and usually the absence of free hydrochloric acid in the gastric juice, a feature which was absent in 1923 in the case described, and which it was unfortunately impossible to investigate in February 1924.

## A CASE OF HYSTERICAL BLINDNESS

By B. G. SCHOLEFIELD, B.M.

JESSIE E., aged 38, unmarried and a violinist by profession, came in on March 17, 1924, suffering from blindness and severe pains in the head and back. She was a thin woman and looked in poor health.

When examined she complained of pain and tenderness in many parts. The application of a stethoscope over the heart, and even light percussion over the left chest, was painful. She could not bear her head to be touched, and there was general abdominal tenderness, though no rigidity. Her periods had been regular, but at these times she complained of severe pains in the pelvis. By conversing with her to keep her attention fixed, a physical examination was possible, and the only abnormality found was enlargement of the heart one inch to the left with a soft hæmic systolic bruit at the apex.

Her pupils both reacted, though somewhat sluggishly, to light, and in using an ophthalmoscope it was possible to place a hand on her head and even press firmly without hurting her. There was no paralysis of the external ocular muscles.

The history of her blindness was that in 1919 objects began to appear to her "in a mauve light." At this time she was

playing the violin a great deal and the acuity of her vision was unaffected. In 1920 the sight of her left eye began to fail and she consulted an oculist, who diagnosed thrombosis of the central vein of the left retina. He prescribed glasses, advised her to have dental treatment, and ended by telling her that there was nothing to be done to her eyes.

A week after seeing the specialist the sight of the left eye failed completely, and in the course of the next two months the right eye also became blind. From that time she was unable to read or do any work at all; the other symptoms already described gradually appeared, and she became a chronic invalid.

When examined at Guy's the inner margin of the right disc was a little indistinct, but otherwise the fundus of that eye appeared normal. The left fundus showed several retinal hæmorrhages, the veins were tortuous and engorged and the arteries thin. She denied any perception of light in the left eye, while the vision of the right appeared to be 3/60 without glasses, and 5/60 with glasses. The left pupil, however, reacted to light independently of the other eye. No reaction to attempted accommodation was obtained in either eye. The field of vision of the left eye was nil, and of the right eye limited to 20° around the optic axis. (The normal field of vision ranges from 50° on the nasal to over 90° on the temporal side.)

It was evident that though her sight was impaired by disease, especially in the left eye, the trouble was mainly hysterical. The reaction of the left pupil showed that that eye was still capable of perceiving light. Her main trouble was that she had lost the power of accommodation, and did not fix her eye on any object, however large, that was held before her.

The method of direct explanation and persuasion was used in treating this case. She was told that her eyes had been damaged by disease four years before, but that what the oculist had meant was, not that the condition of her eyes was hopeless because "there was nothing to be done for them," but that no treatment of the eyes themselves was indicated. It was explained to her that she had lost the power of using her eyes, just as a person with an injured arm that has been splinted loses the use of the arm. In both cases a process of re-education, which might be long and painful, was necessary to restore the muscles and nerves to their normal efficiency. She was then made to fix her eyes on a light which was gradually brought nearer to her. At first there was no effort at accommodation, but after repeated attempts she was made to focus on the light when it was quite close. The eyes then converged normally, and the pupils both reacted. After the first session, lasting an hour, the sight of the left eye, which had previously been nil, had become 6/60, and the sight of the other eye had improved from 5/60 to 6/24.

Several other sessions were necessary before she was able to read. As it was uncertain how much the left eye was permanently damaged, both eyes were used together. Her final

vision with glasses (+ 2 Spherical) was 6/12 and she was able to read print of newspaper size.

### *Commentary*

The main difficulty that had to be met in this case was the apathy and general ill health of the patient. She complained of her head aching whenever she was asked to use her eyes. Even when she had been persuaded that she could with an effort read print, she would not try to do so on her own account, but needed constant urging.

Patients of this class are almost always of a badly balanced temperament, for whom the struggle against environmental difficulties has proved too great. In the present instance, a person enjoying but indifferent health had to work hard for her living. When her eyes began to trouble her, she gave way, and took the line of least resistance. It is not possible to say how much was due to the accidental suggestion by the oculist when she misunderstood his meaning. Instead of trying to see as much as she could, she gave up using her eyes at all. The trouble was not that she could not see, but that she would not look.

In treating these cases it is essential to make sure that the trouble is functional in order to be able to approach them with absolute confidence that they are "curable." Here we were handicapped by the knowledge that there was an undoubted organic basis to the blindness. Various methods of treatment other than that employed were suggested. For instance, it was proposed that atropine drops should be placed in both eyes and that they should then be bandaged up for two days, the patient being assured that at the end of that time sight would have returned. Although such methods may give more dramatic results, the recovery is much less likely to be permanent. They have also the disadvantage that, if the suggestion fails to work, subsequent treatment by any form of psychotherapy is rendered much more difficult.

Finally, having persuaded the patient to use his eyes once more, efforts should be directed towards modifying the environment so that the difficulties to be coped with shall not be so severe. Otherwise similar or new symptoms may subsequently occur.

### A CASE OF ENCEPHALITIS LETHARGICA WITH ONSET OF "ACUTE NEURALGIC TYPE"

By R. B. FAWKES, D.S.O., B.A.

THOMAS J., aged 29, cinema attendant, gave a history of attacks of shooting pain behind the nose and eyes a fortnight

before admission. Following the extraction of teeth the pain had gradually cleared up, but had left demonstrable tenderness in the right temporal region.

On the day before admission—about noon and while standing mixing ice-cream—he experienced a sudden acute pain, starting in the right great toe and passing up the inner side of the foot and leg to a point in the calf about a hand's breadth below the knee. A series of such pains followed in rapid succession, the whole paroxysm taking about 30 to 60 seconds, and recurring at intervals varying from five minutes to over an hour in duration. The description volunteered was very like that of the lightning pain of tabes, save that the paroxysms recurred in the one situation only and left a persistent residual "soreness."

When the patient was seen at Out-Patients, the paroxysms were recurring every few minutes and were causing him literally to writhe in agony on the couch. In the quiescent intervals slight clonic contractions were observed in the adductor muscles of the thigh on the affected side. There was no evidence of local inflammation or tenderness, and the only abnormality was an increased ankle jerk on the right side.

After admission an examination of the cerebro-spinal fluid showed a protein content increased to 0.05. There were no cells, and the Wassermann reaction was negative.

His temperature was 98.8°.

The paroxysms rapidly decreased in severity, though their frequency seemed to be greater the more the patient was conscious that he was being observed.

He was apprehensive of pressure along the calf, but, if his attention were distracted, no tenderness could be demonstrated there.

He slept well the first night with ten grains of aspirin. The next day his pains were almost negligible, his appetite good, his temperature normal, and he himself anxious to get up. He was overheard to discuss with neighbouring patients the symptoms of encephalitis shown by other cases in the ward at the time.

It transpired further in his history that he had left the police force for his present precarious employment, and, although he stated that it was at his own request and on account of difficulty in finding house accommodation near enough to his police duties, all these facts and his general behaviour in the ward prejudiced one against him and his ills.

The fact that he was suffering also from scabies was seized upon as an excuse to discharge him for further investigations to be carried out at Out-Patients.

When he heard his fate he was quite evidently embarrassed. Within two hours he had informed the house-physician that during the previous night he had seen double, and indeed once he had awakened suddenly to see "three"—referring to the single lamp by his bedside.

Finally, when all else failed to shake the decision as to his discharge, he developed purely fictitious pain at the site of the previous day's lumbar puncture. We, that is all of us but one,



were more than ever convinced that we were dealing with a pure case of malingering.

Four days after discharge he was seen at Out-Patients. He then complained of diplopia, and on examination showed (1) paresis of the right external rectus with definite internal strabismus; (2) well-marked ptosis on the left side.

He was notified as a case of encephalitis lethargica and sent home to bed.

The following week he appeared again, but no abnormalities in the central nervous system were demonstrable. He stated that his headaches were gone and he only rarely had periods of diplopia.

He was seen four months later. He then said that he still very occasionally—chiefly when fatigued—had periods of double vision, but he had returned to work. The only abnormality discovered on examination was marked and permanent inequality of the pupils. He still gave one the impression that he was a malingerer, and he had developed an irritating air of self-assurance—not the least objectionable element of which was the frequent smacking of his lips which punctuated his replies to one's questions.

In recording the case and admitting one's original error of diagnosis, it is interesting to speculate whether the mental attitude of the patient, which had led one away from the diagnosis of organic disease, was not, in fact, a further symptom of the disease itself. Unfortunately nothing definite as to change in character can be obtained from the man's friends, but the following points in his favour must in fairness be recorded.

A confidential report from the Metropolitan Police gave him an excellent character and a clear medical history, and entirely substantiated his own version as to why he left the Force. Curiously enough the man was also known to the Clinical Assistant in the Neurological Department as one who had served under him with distinction for eighteen months in the war overseas.

## A CASE OF ANEURYSM OF THE BASILAR ARTERY

By B. G. SCHOLEFIELD, M.B.

WILLIAM B., aged 47, was admitted to Addison Ward on February 21, 1924, for difficulty in swallowing and hiccough.

Except for rheumatism when a child, he had been healthy until February 14, when he caught a cold whilst out motoring. He took to his bed for this, and the next morning complained of severe pain in the right side of the head and neck, and was sick once or twice. His condition improved, however, and he was thinking of getting up again, when during the night of the 18-19th he woke up with renewed pains and found himself suddenly quite unable to swallow. His breathing became distressed, and he complained of blurring of vision.

When seen by his doctor on the 19th, his eyes were in constant nystagmoid movements and deviated to the right, and he had developed a persistent hiccough. He was unable to swallow anything, the actual movement of deglutition being impossible. This condition persisted until the 21st, when he was seen by Dr. Newton Pitt, who sent him up to Guy's.

By the time he was admitted he was considerably collapsed, having had neither food nor drink for over forty-eight hours. He was given a nasal feed, and rectal salines, and after a few hours was much more comfortable. Except that he was constipated and had slight bronchitis, there were no physical signs other than those of a central nervous system lesion. These must be enumerated more fully :—

The discs were normal. The left pupil was larger than the right, but both reacted. The eyes were deviated to the right, and were in constant movement of a concomitant nystagmoid nature which he was unable to control.

The trigeminal, facial and auditory nerves were normal, but he complained of some giddiness. The glossopharyngeal and vagus nerves were much affected, as shown by his difficulty in swallowing.

There was no paralysis of the tongue. The tendon reflexes were more marked on the left side than the right, and there was a somewhat doubtful extensor plantar reflex on the left. Sensation was normal, and muscular co-ordination in the legs was unimpaired. There was some inco-ordination in the arms, especially the left.

Diagnoses of botulism and of encephalitis lethargica were considered. The former was excluded by the absence of any signs of alimentary disturbance. A lumbar puncture was done, and the cerebro-spinal fluid found to be normal, thus making the latter diagnosis improbable. The Wassermann reaction in both blood and cerebro-spinal fluid was negative.

Two days after admission his condition had improved. He was able to control his eyes to a slight extent. The hiccough had stopped, and he was able to swallow sips of water. His voice, however, had become husky, and on laryngoscopy he was found to have paralysis of the right vocal cord. At the same time paralysis of the right side of the palate and weakness of the right side of the face showed themselves.

From February 25 until his death four days later his condition became steadily worse. The pulse, which had remained at 90, started to rise slowly, reaching 140 on the last day. His respiration became very shallow, and the bronchitis more marked, until he was cyanosed and oxygen had to be administered. Bronchopneumonia developed later, and the patient died on the morning of the 29th.

At the autopsy a swelling of the right vertebral and basilar arteries was found, which on section proved to be a dissecting aneurysm starting low down on the right vertebral, and spreading gradually upwards, occluding the lumen of the vessel as it spread.

*Commentary*

Although the case had been diagnosed by Dr. Newton Pitt before admission as "a lesion in the neighbourhood of the medulla," the presence of an aneurysm had not been suspected. The Wassermann reaction was negative. The heart was not enlarged and the blood-pressure only 150 mm. The origin of the aneurysm was lower down in the cord, but there was very little atheroma of the arteries generally.

Reviewing the case in retrospect, with the post-mortem findings known, it is interesting how closely the observed symptoms and signs can be fitted in. The early pain in the neck on the right side would be due to pressure on the upper posterior nerve roots. As the aneurysm spread upwards between the walls of the vertebral artery it would reach the basilar and occlude this vessel comparatively suddenly. This was shown by the sudden affection of the vagus, glossopharyngeal and vestibular nerves. The escape of the hypoglossal is difficult to understand. Later again the impairment of these nerves diminished to some extent, through improvement perhaps in the collateral circulation, but at the same time the damage spread further up to involve the seventh nerve. It is doubtful if the oculomotor nuclei were directly involved; the eye symptoms were probably due to reflex action from the vestibular nuclei. The hiccoughing, which was a marked symptom at one stage of the case, was probably due to irritation of some part of the vagus centre.

## A CASE OF TRAUMATIC CEREBRAL ŒDEMA

By W. R. SPURRELL, B.Sc.

CISSIE —, a Russian, æt. 35, was admitted on February 17, 1924, suffering from Jacksonian fits. She had had typhus and measles when in Russia as a child, but had been quite healthy since. She had two children, eight and six years old, and had had one miscarriage; none of her pregnancies had been complicated by nervous symptoms and there was no family history of any nervous disorder. At the time of admission the patient was five months pregnant.

On February 6 the patient was kneeling in the fireplace when a heavy overmantel and mirror fell and struck her on the right side of the head; she did not lose consciousness and there were no external signs of injury. For the next week she was rather dull and irritable, complaining continually of headache. During the night of February 13 she had an attack of twitching and mumbling in her sleep; she was well on the following day, but on the evening of February 15 she suddenly stopped still, her face was twisted to the left, she became rigid and made

strange noises. She did not fall to the ground, but soon recovered. During the evening she had three more such attacks, which left her with "thick speech." On February 16 she had a series of fits and became comatose, in which condition she remained up till the time of admission.

On admission she was comatose and had a left hemiplegia with some spasticity; she resented interference, moving her right arm and leg vigorously and muttering incoherently when stimulated. Ankle clonus, extensor plantar reflex and increased tendon reflexes were present on the left side; both abdominal reflexes were absent and the remainder of the right reflexes were normal. The left facial nerve was the only cranial nerve obviously paralysed. The optic discs could not be seen, as the patient rolled her eyes. As far as could be determined, sensation appeared equal on both sides. The urine had S.G. 1010 and contained a little reducing substance as the only abnormality. The blood pressure was—systolic, 120 mm. Hg., diastolic, 85 mm. Hg.; pulse 108; temperature 97° F.; respirations 28.

The patient had nineteen fits in the twenty-four hours following admission; each fit began with opening of the eyes, conjugate deviation to the left, followed by drawing of the mouth to the left and then the head; the left arm then became stiff and began to twitch, then the left leg, and then convulsions spread all over the body. During the attacks the patient became deeply cyanosed. Occasionally between fits she uttered a few intelligible words, such as a request for water, but the lack of a sufficiently expert linguist probably made her appear more incoherent than in actual fact.

The diagnosis of localised sub-dural hæmorrhage was made on the evidence of definite Jacksonian attacks developing after a latent period of ten days from the original blow. Eclampsia was suggested, but the definite localisation combined with a normal blood-pressure and urine served to rule it out.

No definite signs of improvement appeared, so on February 18 Mr. L. Bromley operated: a right temporal osteo-plastic flap was turned down and the dura mater incised. A moderate degree of cortical bulging was found, indicative of a slightly increased pressure; the whole of the cortex visible was markedly œdematous, but no hæmorrhage or localised lesion was found; the flap was replaced. Following the operation the patient was maniacal for some days; at the end of a week she was sleeping quietly and talking rationally. She made an uninterrupted recovery and was discharged on March 24, with occasional headaches as her only symptom. Since her operation she had not had a single fit.

Seen eight months after the operation she showed no physical signs of any derangement of the nervous system. She had occasional headaches, but they were not severe enough to interfere with her ordinary daily work. She had been delivered of a full-time child four months after the operation and the baby was thriving.

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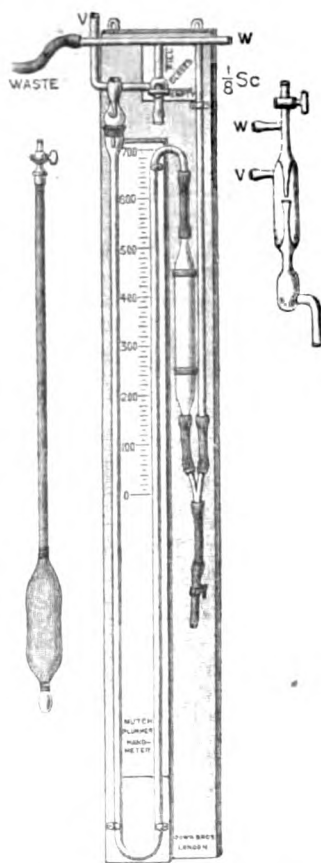
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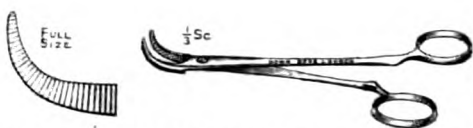
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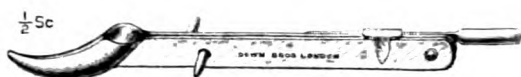
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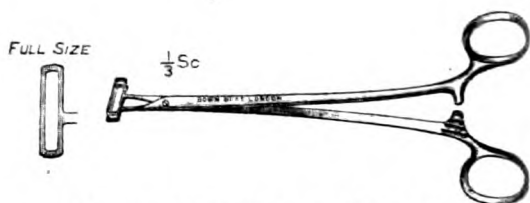
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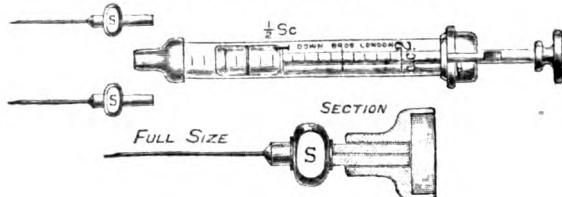
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